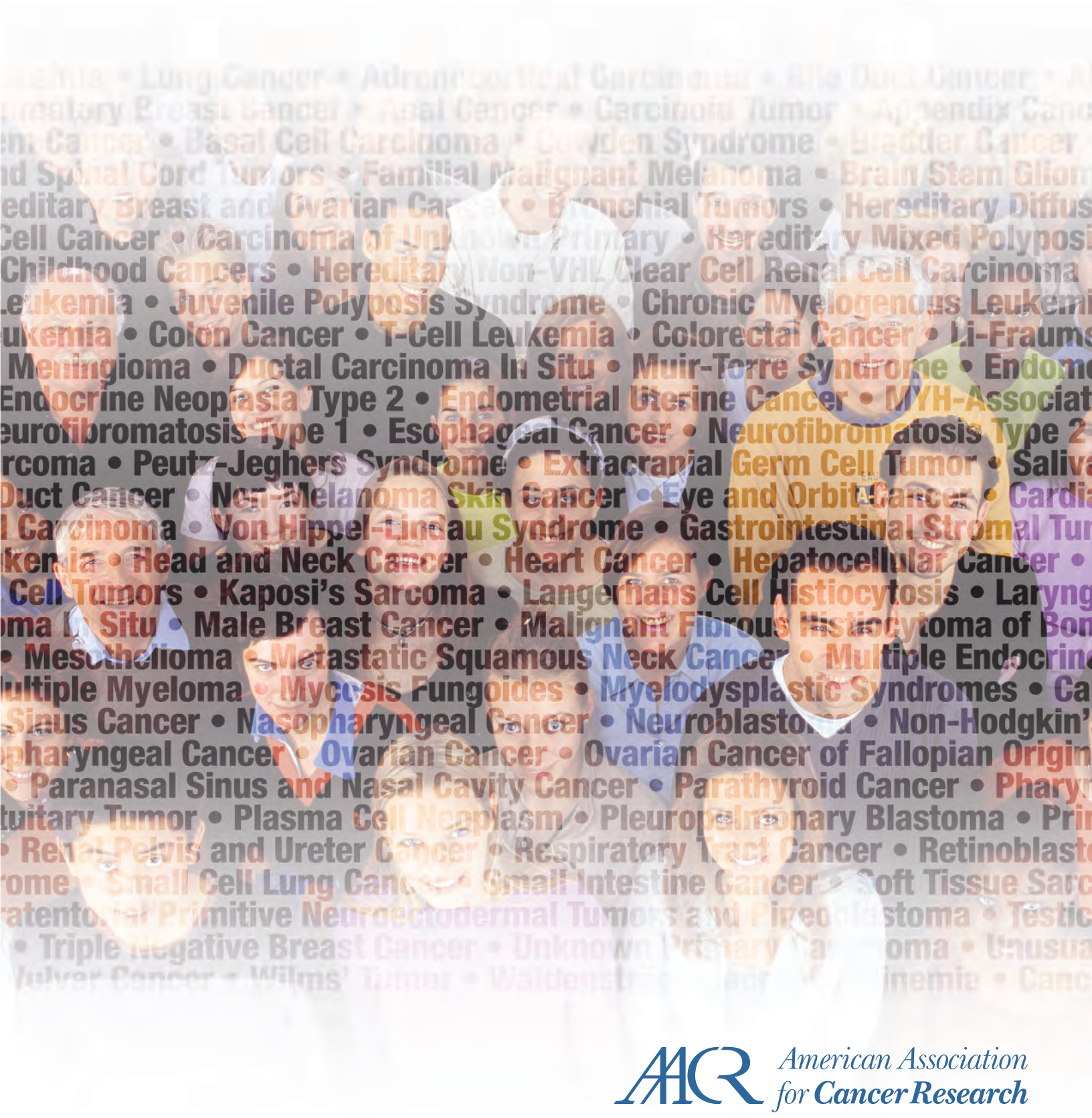
AACR Cancer **Progress** Report **2011**

Transforming Patient Care Through Innovation



American Association for Cancer Research

www.cancerprogressreport.org • www.aacr.org

About the Cover

The cover of the first-ever AACR Cancer Progress Report, which chronicles the transformation of research discoveries from the past decades into improvements in patient care, represents some of the 12 million living cancer survivors as a result of these transformations. The cover also depicts but a fraction of the over 200 individual diseases that make up what we call cancer. Despite this progress, 1 out of every 2 men, and 1 out of every 3 women in the U.S. will be diagnosed with cancer in their lifetimes, as represented by the glossy individuals on this page and the inside back cover. On behalf of these individuals and their loved ones, the AACR has written this report to urge Congress to provide sustained funding increases for life-saving cancer and biomedical research, particularly that which is supported by the National Institutes of Health and the National Cancer Institute.

AACR Cancer **Progress** Report
2011

Transforming Patient Care Through Innovation

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Cancer Progress Report Writing Committee

Co-Chairs

Elizabeth H. Blackburn, Ph.D,
AACR Immediate Past President
Nobel Laureate
Morris Herzstein Professor of Biology and Physiology
Department of Biochemistry and Biophysics
University of California, San Francisco, San Francisco, CA

Judy E. Garber, M.D., M.P.H.
AACR President
Director, Center for Cancer Genetics and Prevention
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School, Boston, MA

George F. Vande Woude, Ph.D.
Chair, AACR Council of Scientific Advisors
Distinguished Scientific Fellow and Professor
Laboratory of Molecular Oncology
Van Andel Institute, Grand Rapids, MI

William S. Dalton, Ph.D., M.D.
Chair, AACR Science Policy and Legislative Affairs Committee
President/Chief Executive Officer and Center Director
H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Anna D. Barker, Ph.D.
Member, AACR Science Policy and Legislative Affairs Committee
Director, Transformative Healthcare Networks; Co-Director Complex Adaptive Systems Initiative; Professor, School of Life Sciences
Arizona State University, Tempe, AZ

Margaret Foti, Ph.D., M.D. (h.c.)
Member, AACR Executive Committee and Board of Directors
Member, AACR Science Policy and Legislative Affairs Committee
Chief Executive Officer
American Association for Cancer Research, Philadelphia, PA

Committee Members

Julian Adams, Ph.D.
President of Research and Development
Infinity Pharmaceuticals, Cambridge, MA

Napoleone Ferrara, M.D., Ph.D.
Genentech Fellow, Tumor Biology and Angiogenesis
Genentech, Inc., South San Francisco, CA

Richard B. Gaynor, M.D.
Vice President, Oncology Business Unit
Eli Lilly and Company, Indianapolis, IN

Waun Ki Hong, M.D.
AACR Past President
Head, Division of Cancer Medicine
The University of Texas, MD Anderson Cancer Center, Houston, TX

Tyler Jacks, Ph.D.
AACR Past President
Director, David H. Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology, Cambridge, MA

Michael Karin, Ph.D.
Professor, Department of Pharmacology
University of California, San Diego, La Jolla, CA

Gloria M. Petersen, Ph.D.
Consultant and Professor, Clinical Epidemiology
Mayo Clinic College of Medicine, Rochester, MN

Consultants

Lodovico Balducci, M.D.
Leader, Senior Adult Oncology Program
H. Lee Moffitt Cancer and Research Institute, Tampa, FL

Donald A. Berry, Ph.D.
Chairman and Professor, Department of Biostatistics
The University of Texas MD Anderson Cancer Center, Houston, TX

Yves A. DeClerck, M.D.
Professor of Pediatrics, Biochemistry, and Molecular Biology
University of Southern California
Children's Hospital Los Angeles, Los Angeles, CA

Olivera J. Finn, Ph.D.
Chair and Distinguished Professor of Immunology
Department of Immunology
University of Pittsburgh School of Medicine, Pittsburgh, PA

Ernest T. Hawk, M.D., M.P.H
Vice President and Division Head
Boone Pickens Distinguished Chair for Early Prevention of Cancer,
Division of Cancer Prevention and Population Sciences
The University of Texas MD Anderson Cancer Center
Houston, TX

Peter A. Jones, Ph.D., D.Sc.
AACR Past President
Director, University of Southern California Norris Comprehensive Cancer Center
Los Angeles, CA

Danielle Lenahan, RPh, M.B.A.
Pharmacy Manager, Penn Medicine at Rittenhouse
University of Pennsylvania, Philadelphia, PA

Suzanne Ostrand-Rosenberg, Ph.D.
Professor of Biological Sciences
Robert and Jane Meyerhoff Chair of Biochemistry
University of Maryland, Baltimore, MD

Kenna Mills Shaw, Ph.D.
Deputy Director, The Cancer Genome Atlas Program Office
National Cancer Institute, Bethesda, Maryland

Cornelia M. Ulrich, Ph.D.
Director and Professor, Division of Preventive Oncology
National Center for Tumor Diseases German Cancer Research Center, Heidelberg, Germany

Robert H. Vonderheide, M.D., D.Phil.
Associate Professor of Medicine
Abramson Family Cancer Research Institute
University of Pennsylvania School of Medicine
Philadelphia, PA

Danny R. Welch, Ph.D.
Professor of Cancer Biology
Kansas University Cancer Center
Kansas City, KS

Harald zur Hausen, D.Sc., M.D.
Nobel Laureate
German Cancer Research Center
Heidelberg, Germany

AACR Staff

Shawn Sweeney, Ph.D.
Project Leader
Senior Program Administrator
Philadelphia, PA

Jon Retzlaff, M.B.A., M.P.A.
Managing Director, Science Policy and Government Affairs
Washington, DC

Pamela Bradley, Ph.D.
Director, Science Policy
Washington, DC

Mary Lee Watts, M.P.H., R.D.
Director, Government Relations
Washington, DC

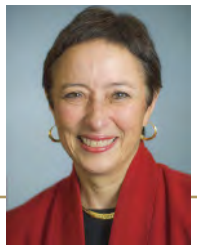
Kelsey Johnson, M.P.A.
Associate Policy Analyst
Washington, DC

Paul Driscoll
Director, Marketing and Creative Services
Philadelphia, PA

Nicolle Rager Fuller
Illustrator
Sayo-Art, LLC
Bellingham, WA

A Message from the AACR


Blackburn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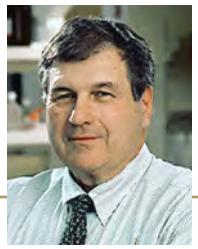
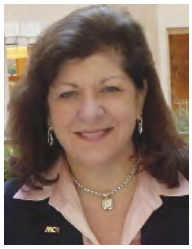

Vande Woude


Dalton


Barker


Foti

This year marks the 40th anniversary of the signing of the National Cancer Act of 1971. This legislation was historic and dramatic in its consequences because it focused the country's attention on the vital need to conquer this disease at the earliest possible time.

The American Association for Cancer Research (AACR), and its 33,000 laboratory, translational, and clinical researchers; other health care professionals; and cancer survivors and advocates in the United States and more than 90 other countries, believe it to be a fitting time not only to commemorate the advances in cancer research that have been made to date, but also to paint a picture of where the science is leading us.

Today the United States leads the world in biomedical research. The impressive progress highlighted in this report, and most importantly that which is reflected in the 12 million cancer survivors alive today in the U.S. alone, is due in large part to the wisdom that the Congress has shown by its strategic investments in the research grant programs of the National Institutes of Health (NIH) and the National Cancer Institute (NCI). The many breakthroughs that are transforming the prevention, detection, diagnosis, and treatment of cancer represent an unprecedented return on investment that can be measured in lives saved, higher quality of life for cancer survivors, and enormous economic benefit to our country and indeed the world.

Recent advances in understanding cancer at the molecular level have set the stage for a new era of cancer medicine, in which cancer patients will be treated based on their molecular profile. This report provides "snapshots" of some of the key scientific and clinical advances against cancer that have brought us to this point, as well as a glimpse of what the future could hold for cancer patients and their families provided that research is supported with the necessary resources.

Hard-fought progress over the past 40 years by the entire cancer research community — laboratory researchers, physician-scientists, clinicians, cancer survivors and patient advocates, citizen activists, philanthropic organizations, scientific and clinical societies, government, academia, the pharmaceutical and biotechnology industries, and cancer patients themselves — now provides unprecedented opportunities to translate current discoveries of the critical molecular changes that drive cancer into improved patient care. Although we are on the cusp of furthering our ability to exploit these exciting findings for the benefit of patients, our ability to do so will depend on a strong commitment by Congress to provide the necessary funding for the NIH and NCI.

Millions of current and future cancer patients are relying on us all to change the face of cancer on their behalf. We should ask no less of ourselves at this critical juncture. Cancer touches all of us, whether directly as a cancer patient or through the diagnosis of loved ones. Therefore, we need to intensify our efforts to eradicate cancer as a major threat to American lives.

The AACR recognizes that Congress is being called upon to make difficult decisions as its members strive to address the Nation's fiscal problems. These demanding times emphasize the need to make fiscal decisions that benefit every American. Sustaining our investments in cancer and biomedical research is a bipartisan strategy that will pay off in lives saved, improvements in public health, continued innovation, and economic growth.

The AACR wishes to extend thanks to every member of Congress – past and present – who has stood with us in this long and difficult challenge to defeat cancer. We stand unified and ready to work with our Nation's policymakers and the entire biomedical research community to hasten the prevention and cure of cancer.

Elizabeth H. Blackburn, Ph.D.
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Margaret Foti, Ph.D., M.D. (h.c.)
Chief Executive Officer

About the American Association for Cancer Research

The mission of the American Association for Cancer Research (AACR) is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest scientific organization dedicated to the advances in cancer research for the benefit of cancer patients.

Its membership includes 33,000 laboratory, translational, and clinical researchers who are working on every aspect of cancer research; other health care professionals; and cancer survivors and patient advocates in the United States and more than 90 countries outside the U.S. The AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, etiology, early detection, diagnosis, and treatment of cancer through innovative scientific and educational programs and publications. It funds innovative, meritorious research grants to both senior and junior researchers, research fellowships for scholars-in-training, and career development awards.

The AACR Annual Meeting attracts more than 18,000 participants who share the latest discoveries and new ideas in the field. Special Conferences throughout the year present novel data across a wide variety of topics in cancer research, ranging from the laboratory to the clinic to the population. The AACR publishes seven major peer-reviewed journals: *Cancer Discovery*; *Cancer Research*; *Clinical Cancer Research; Molecular Cancer Therapeutics*; *Molecular Cancer Research; Cancer Epidemiology, Biomarkers & Prevention; and Cancer Prevention Research*. In 2010, the AACR's scientific journals received 20 percent of the total number of literature citations in oncology.

The AACR also publishes a magazine, *Cancer Today*, for cancer patients, survivors, patient advocates, and their families and caregivers that includes essential, evidence-based information and perspectives on progress in cancer research, survivorship, and healthy lifestyle.

A major goal of the AACR is to educate the general public and policymakers about the value of cancer research in improving public health, the vital importance of increases in sustained funding for cancer research, and the need for national policies that foster innovation and progress in the field.

AACR Headquarters
615 Chestnut Street, 17th floor
Philadelphia, PA 19106-4404
Telephone: (215) 440-9300
Fax: (215) 440-9313

AACR Office of Science Policy and Government Affairs
1425 K Street, NW, Suite 250
Washington, DC 20005
Telephone: (202) 898-6499
Fax: (202) 898-0966

Executive Summary

Background

With the historic passage of the National Cancer Act in 1971, the President, Members of Congress, and the general public came together to set the Nation on a course to conquer cancer. This unprecedented action occurred at a time of great optimism that America could accomplish anything. In 1971, we had limited knowledge of this dreaded disease, and treatment options were few. But since that time, cancer researchers have worked relentlessly to understand and control this disease that our citizens still fear the most.

As a result of the dedicated work of thousands of cancer and biomedical researchers employing ever-advancing technologies, we have made great progress. We now understand in detail that cancer is complex at every level – ranging from populations to the very genes and molecules that drive a patient's cancer. Cancer is a biological process gone awry. It is, in fact, not a single disease, but more than 200 diseases – all of which have different causes and require different treatments. By harnessing decades of laboratory, translational, and clinical research to accelerate breakthroughs, cancer research has steadily developed and improved therapeutic approaches to the point where today, more than 12 million Americans are cancer survivors; and cancer mortality rates have steadily declined since 1990. However, this progress does not change the fact that we face a future where cancer will soon become the number one killer of Americans – and this trend is also expected to occur globally.

Although these projected increases in the number of new cancer cases and the sheer complexity of cancer are daunting, we have never been better positioned to capitalize on our hard-fought understanding of cancer – what causes it – what drives it. We now understand that changes in an individual's genes drive cancer initiation and development, and are entering an era when every patient's tumor can be characterized at the molecular level. With this new knowledge, therapies specifically targeting the molecular defects within the tumor are almost commonplace.

This is a defining time in America's commitment to finally defeat cancer. Because of unimagined progress – and a vision of what is now possible – there is enormous optimism and new hope that we can achieve this goal. For the first time since the passage of the National Cancer Act, this report to Congress from the American Association for Cancer Research seeks, insofar as is possible, to capture the breadth and depth of advances that have brought us to this inflection point in the cancer field. As we enter this era where progress will most certainly accelerate, we commit ourselves to continue to chronicle the spectacular breakthroughs in cancer research; and urge all Members of Congress to preserve support for our national effort to conquer this horrific disease that affects so many.

Progress in Understanding Cancer

Funds provided by Congress since 1971 to the National Institutes of Health (NIH) and the National Cancer Institute (NCI) have enabled extraordinary progress against cancer, and in doing so have saved countless lives while catalyzing the development of the biotechnology industry and economic growth in America. We now have a deep understanding of the fundamental nature of cancer, and why and how cancer develops and spreads throughout the body. Research has revealed that changes or mutations in our genes are the cause of most if not all cancers. Boosted by the completion of the large-scale publicly funded Human Genome Project, more than 290 genes related to the cause of cancer have been discovered to date. This list of cancer-related genes continues to grow as advanced technologies and other similar large-scale projects supported by public funds facilitate the identification of all of the relevant genomic changes in different types of cancer by comparing the DNA in a patient's normal tissue with that of the DNA in the tumor.

The identification of genes that are mutated in cancer cells has pinpointed two key classes of cancer genes: oncogenes, which often drive the uncontrolled cell growth that is a hallmark of cancer, and tumor suppressor genes, which function in normal cells to safeguard the integrity of the genome. We now understand that oncogenes and tumor suppressor genes often malfunction in cancer cells. As a result of unrepaired damage to their DNA, this leads to disruptions in the networks of cellular proteins that control cell growth.

We have also learned that cancer is more complex than just these two types of genes – and that something as seemingly simple as how DNA is chemically modified and packaged in a cell (called epigenetics) can regulate the vast networks that control cellular functions. Further, the tumor's environment regulates cell behavior – and can support both tumor growth and the spread of cancer to other parts of the body. Metastasis remains one of the toughest problems in cancer research and is the major source of the morbidity and mortality associated with cancer. Finally, cancer cells have the uncanny ability to inactivate the patient's immune system in order to avoid the body's attempt to eliminate the tumor cells.

These major discoveries in the biology of cancer are being translated daily into an ever-expanding array of new cancer therapies, diagnostics, and preventives. They define our current standard of care and have extended the lives of millions of Americans. Unfortunately, for all of these scientific successes, we are continually humbled by cancer's ability to defy expectations and change and adapt in response to treatment. This adaptability is largely a result of the presence of different types of cancer cells within the same tumor, known as tumor heterogeneity, caused by the rapidly mutating cancer genome. Tumor heterogeneity ultimately leads to drug resistance and metastasis. Clearly, cancer's complexity still stands as a major challenge in cancer research.

Setting the Standard of Care

It is estimated that at least 50% of cancers that occur in the U.S. each year are preventable. This fact underscores the need for continued research to inform educational campaigns and programs that can encourage and help individuals change their behaviors. In fact, some of the greatest reductions in cancer mortality have resulted from the implementation of public health measures to mitigate tobacco use, radiation exposure, other environmental and workplace carcinogens, certain hormones, obesity and related changes in energy balance, and infectious agents, all of which play a major role in causing cancer.

Finding a tumor early makes it more likely that it can be treated successfully with fewer side effects. Fueled by advances in our molecular understanding of cancer, population-based screening programs have enabled routine screening and early detection for the prevention of cervical, breast, prostate, and colorectal cancers. As a result, the 5-year survival rates for cervical, breast, and prostate cancers are well over 90%, and mortality due to colorectal cancer continues to decline.

Over the past four decades we have also seen important advances in the triad of cancer patient care—chemotherapy, surgery, and radiation—as well as in the provision of supportive or palliative care. New types and combinations of cytotoxic chemotherapy drugs have led to major increases in survival, and frequently to cures, of patients with childhood acute lymphoblastic leukemia, Hodgkin's disease, aggressive lymphomas, and testicular cancers. Advances in surgical techniques and radiotherapy permit more complete removal of solid tumors with minimal damage to the surrounding tissue – which improves both quality of life and survival.

These advances define our current standard of care; however, recent research is pointing to a whole new approach based on our understanding of the molecular

defects that drive cancer. This new knowledge is already providing innovative targeted treatments that promise to revolutionize the current and future standard of care for cancer patients

Personalized Cancer Medicine

Researchers have created a powerful knowledge base about cancer. It is now possible to know the molecular changes in cancer and how these impact drug design and the clinical trials to evaluate new targeted agents. As we continue to build our knowledge base, we are transforming findings into new cancer treatments at an accelerating pace. It is this transformation in knowledge, driven in large measure by advanced technologies, that promises to change the paradigm of cancer medicine. We are moving away from an era of one-size-fits-all cancer care to the exciting realm of personalized cancer medicine, also called molecularly based medicine, precision medicine, or tailored therapy, where the molecular makeup of the patient and the tumor will dictate the best therapeutic strategy, in an effort to increase survival.

Previously the organ of origin, such as lung, brain, or breast, and so on, defined an individual's cancer; now it is defined by the intrinsic molecular changes driving the cancer, irrespective of its location. For some cancers, we know that specific molecular defects cause over-activation of the signaling networks that control normal cellular function and growth. This, combined with advances in biology, chemistry, and computational modeling, has made it possible to identify and develop new drugs designed specifically to block the malfunctions that drive cancer cells to proliferate out of control. These targeted drugs, which are much less toxic, stand in stark contrast to cytotoxic chemotherapy drugs, which affect all cells – killing both cancerous and healthy cells. There are now 32 FDA-approved drugs that target tumor cells with far fewer side effects. For example, the drug imatinib (Gleevec), which targets a specific chromosomal defect found in 95% of all chronic myelogenous leukemia (CML) patients, has transformed this disease from a death sentence into a chronic condition with a 5-year survival of 95%.

We have also witnessed the development of an entirely new classes of drugs, including therapeutic antibodies. One such drug, trastuzumab (Herceptin), has decreased recurrence and improved survival for the nearly 20% of breast cancer patients whose tumors over-express a specific molecular target, the human epidermal growth factor receptor 2 (HER2). In addition, other molecular defects, such as epigenetic processes, the tumor's blood supply, and the patient's immune system, are now successfully and effectively treated using new therapies.

Perhaps more importantly, our increasing understanding of the unique biological processes of cancer cells has also begun to provide a molecular understanding of a patient's risk of developing cancer. In some cases, the presence of mutations in genes like BRCA1 and 2, which are inherited, greatly increases a person's risk for certain types of cancer – including breast and ovarian cancer in women and aggressive forms of prostate cancer in men. At the present time, there is no way to correct these inherited cancer gene mutations; however, the knowledge that individuals are in a high-risk category empowers them to take actions that reduce their risk.

This increased understanding of the molecular basis of cancer within specific high-risk patients has opened up the field of chemoprevention, where patients are given drugs that prevent the disease from developing or recurring. There are approximately 150 chemoprevention clinical trials underway to identify agents that can reduce cancer incidence in high-risk populations. This is an area of great promise. The pursuit of molecularly based strategies to identify high-risk patients and intervene to stop cancer before it starts deserves our most intensive efforts and must become one of our highest priorities.

The Future: Fully Realizing the Potential of Our Current Opportunities

Unquestionably, we stand at a pivotal juncture in our Nation's commitment to conquer cancer. Realizing this goal will require focusing on supporting innovative research; developing a network of tissue banks of high-quality, clinically defined tissue samples, or biospecimens; deploying informatics platforms to store, manage, and analyze what is already a data overload from genomics and the molecular sciences; enabling the convergence of the physical sciences and engineering with cancer biology to further unravel the complexity of cancer; capitalizing on and enabling the development of advanced technologies; and melding the enormous power of large-scale, collaborative team science with individual investigator initiated research.

Realizing today's promise of a future where personalized cancer medicine becomes the norm will require that government, academia, the pharmaceutical and biotechnology industries, philanthropic organizations, scientific and clinical societies, survivor and patient advocacy groups, and patients all work together collaboratively to create synergistic partnerships and novel research models.

Technology is moving at a dizzying pace – and it is difficult to predict which of the advanced technologies and new approaches will most significantly impact cancer research and improve patient care. Nanotechnology, stem cells, cancer metabolism, the microbiome, and non-coding RNAs, among others, all represent paradigm-shifting technologies and research areas that could dramatically accelerate advances against all types of cancer.

We live in an unprecedented time of scientific opportunities, and our commitment to prevent and cure cancer has never been stronger. Researchers are moving outside their traditional landscape of knowledge into an arena of extraordinary change in cancer science and medicine.

Innovations in cancer and biomedical research are enabling a scientific revolution that will facilitate the participation of patients in personalized cancer medicine. These life-saving therapeutic and preventive strategies augur well for further reductions in cancer incidence and mortality.

Inspired by the excitement of our past discoveries, researchers and their partners in the cancer research community possess the steadfast resolve to seize the day and forge ahead to the finish line – to the day when cancer is removed as a major threat to our Nation's citizens and to future generations. Realizing this bright future of cancer prevention and cures requires that Congress and the general public stand firm in their commitment to the conquest of cancer. Otherwise, we will fail in our ability to capitalize on the opportunities before us to significantly reduce the toll that cancer takes on American lives, and it will produce a devastating impact on our Nation's economy, consequences which are unimaginable and intolerable.

"The Brown women are a living testament to the power of scientific research to significantly reduce the ravages of this insidious disease. Generation by generation, we are evidence of how far medical research has taken us, and I believe in its power to someday put an end to this cycle of disease once and for all."

Zora Brown
3-Time Cancer Survivor

The Status of Cancer

Today we know that cancer, which is in fact not one disease but more than 200 different diseases, is much more complex than what could have been imagined in 1971 when the United States Congress passed the National Cancer Act. Fortunately, investments in cancer and biomedical research, in particular those supported during the past four decades by public funds through the National Institutes of Health (NIH) and the National Cancer Institute (NCI), have accelerated the pace of discovery and the development of new and better ways to prevent, detect, diagnose, and treat cancer in all age groups. The results of these investments are cures for some patients with certain types of cancer and higher quality, longer lives for those patients whose cancers we cannot yet prevent or control.

Between 1990 and 2007, death rates in the U.S. for all cancers combined decreased by 22% for men and 14% for women, resulting in 898,000 fewer deaths from the disease during this time period[1]. Today, more than 68% of adults are living 5 or more years after initial diagnosis, up from 50% in 1975; and the 5-year survival rate for all childhood cancers combined is 80% vs. 52% in 1975[2]. As a result of our Nation's investments in cancer and biomedical research, about 12 million cancer survivors are alive in the U.S. today, and 15% of these cancer survivors were diagnosed 20 or more years ago[3].

Our unprecedented progress against cancer is the result of extraordinary advances in research, combined with both visionary public health policy and the passionate work of survivor and patient advocates. For example, the translation of fundamental discoveries from the laboratory to the clinic has produced over 30 FDA-approved molecularly targeted drugs that are less toxic and more effective in treating a number of cancers. In addition, the U.S. Surgeon General's historic 1964 Report on Smoking and Health concluded that scientific evidence proved a causal relationship between smoking and cancer, putting into motion the development of a policy framework that has resulted in a reduction in the number of smokers in the U.S. from 42% of the population[4] in 1965 to 20% today[5]. This has saved millions of lives that would otherwise have been lost not only to lung cancer, but also to the 17 other types of cancer directly related to tobacco use[6].

Table 1: Cancer Incidence and Death Rates from (1990-2006)[7]

Cancer	Total est 2011 Incidence	Total est 2011 deaths	Change in Death Rates 1990-2006 Female		Male	
All Malignant Cancers	1,596,670	571,950	⬇⬇	12.3	⬇⬇⬇	21
Breast	232,620	39,970	⬇⬇⬇	28.3		N/A
Brain & Nervous System	22,340	13,110	⬇⬇	17.6	⬇⬇	14.1
Cervix Uteri	12,710	4,290	⬇⬇⬇⬇	30.7		N/A
Colorectum	101,340	49,380	⬇⬇⬇	28.4	⬇⬇⬇⬇	33.4
Esophagus	16,980	14,710	⬇	0.2	⬆	9.7
Hodgkin Lymphoma	8,830	1,300	⬇	0.5	⬇⬇⬇⬇	34.7
Kidney & Renal Pelvis	60,920	13,120	⬆	0.1	⬇	6.9
Leukemia	44,600	21,780	⬇⬇	14.6	⬇	10.3
Liver & Bile duct	26,190	19,590	⬆⬆⬆	30	⬆⬆⬆⬆	46.5
Lung & Bronchus	221,130	156,940	⬆	6.8	⬇⬇⬇	25.5
Melanoma of the skin	70,230	8,790	⬇	0.1	⬆	7.1
Myeloma	20,520	10,610	⬇	1.4	⬇	9.7
Non-Hodgkin Lymphoma	66,360	19,320	⬇	1.4	⬇⬇	15.6
Oral Cavity & Pharynx	39,400	7,900	⬇⬇⬇⬇	31.6	⬇⬇⬇⬇	32.6
Ovary	21,990	15,460	⬇	10.2		N/A
Pancreas	44,030	37,660	⬆	2.1	⬇	0.1
Prostate	240,890	33,720		N/A	⬇⬇⬇⬇	38.9
Stomach	21,520	10,340	⬇⬇⬇⬇	34	⬇⬇⬇⬇	43.1
Urinary Bladder	69,250	14,990	⬇	0.1	⬇	5

Decrease		Increase	
⬇	0-10	⬆	0-10
⬇⬇	11-20	⬆⬆	11-20
⬇⬇⬇	21-30	⬆⬆⬆	21-30
⬇⬇⬇⬇	30+	⬆⬆⬆⬆	30+

Because of the enormous complexity of cancer, progress against certain cancers has been difficult (see **Table 1**, p.13). Pancreatic, brain, and lung cancers still represent major killers–but new insights into their function and control at the molecular level are informing the development of a new generation of specific diagnostic and treatment strategies that hold promise for increased clinical efficacy and survival.

Unfortunately, despite significant advances in cancer research that have resulted in improvements in survival for many cancers, more than 570,000 people will die each year from the disease, which is more than 1 person every minute, every day[1]. In fact, 1.6 million Americans are diagnosed every year with cancer, and approximately 1 out of every 3 women and 1 out of every 2 men will develop cancer in their lifetimes[1]. It is no wonder that a cancer diagnosis remains the worst fear of Americans as determined by an AACR survey conducted in 2000. Since that time, an AP-LifeGoesStrong.com poll[8] has confirmed this finding among older adults, and in 2010 a Cancer Research UK poll showed that 20% of Europeans of all ages consider cancer their biggest fear[9].

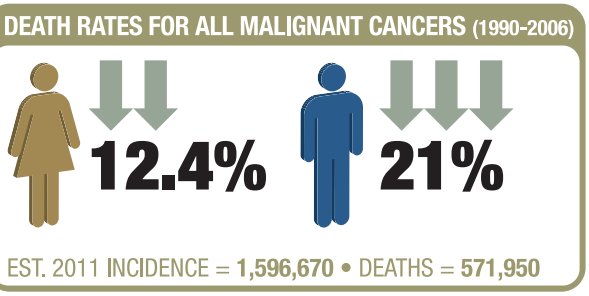
NIH Support of Intramural and Extramural Research

Intramural research accounts for approximately 10% of the NIH budget. It is performed in NIH laboratories and involves about 5,300 researchers and staff, in addition to 5,000 trainees.

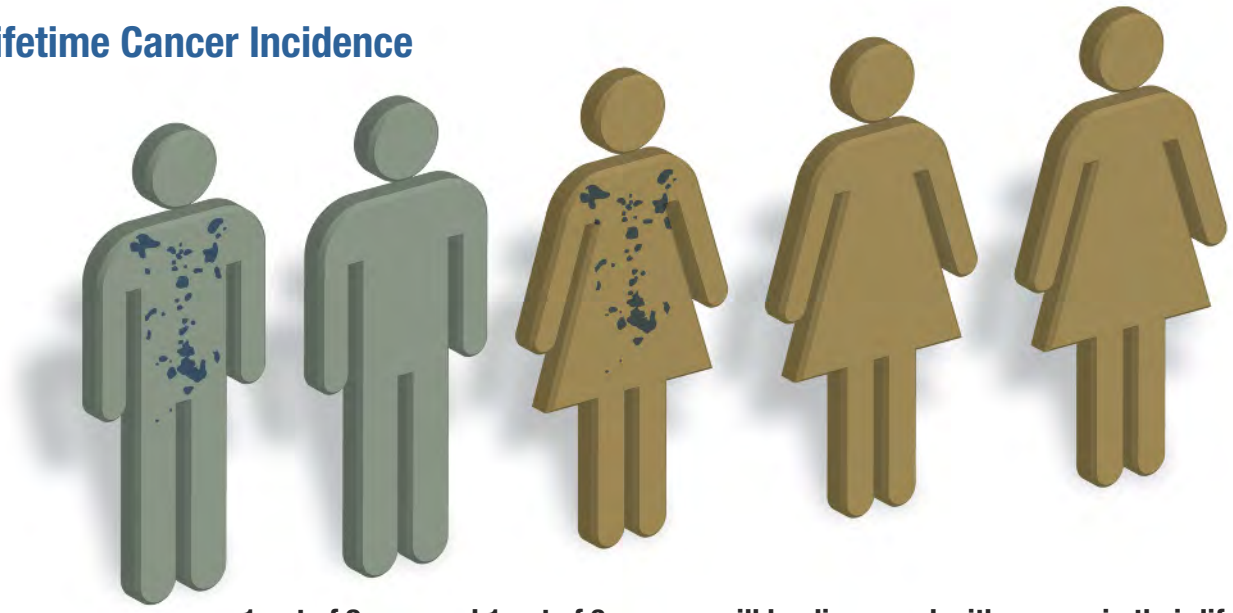
The vast majority of the NIH budget—more than 80%—is competitively awarded to researchers across the Nation in the form of extramural research grants. These applications are reviewed using a rigorous two-tiered system of peer review that evaluates the scientific and technical merit as well as the program relevance of each research proposal.

NIH funds support the work of more than 325,000 researchers and research personnel at more than 3,000 universities, medical schools, medical centers, teaching hospitals, small businesses, and research institutions in every state.

NIH funding not only results in scientific discoveries, but it also generates new economic activity and employment in the communities that receive its funds.



Lifetime Cancer Incidence



1 out of 2 men and 1 out of 3 women will be diagnosed with cancer in their lifetimes.

Further, cancer is a looming health care crisis. Although cancer is diagnosed in all age groups, over 60% of all cancers occur in the 13% of the population over the age of 65. This group will comprise 20% of the population by the year 2030 and will account for more than 70% of all cancer diagnoses[10]. Thus, because of this fact alone, the Nation's cancer burden is expected to rise steeply in the next 20 years. Also, cancer represents a huge economic burden, amounting to total costs of $263.8 billion in the U.S. alone in 2010. It is therefore urgent that we continue to research and develop successful preventive interventions and treatments.

There is no doubt that the conquest of cancer represents a significant challenge for the international community of cancer researchers. Cancer rates are on the rise worldwide, with cancer expected to claim the lives of 17 million people by 2030[11] and predicted to become the No. 1 killer worldwide in the very near future. Moreover, of all causes of death worldwide, cancer has the greatest economic impact from premature death and disability. This global economic toll is 20% higher than from any other major disease, at $895 billion annually[12], not including the direct costs of treating cancer. Collaborations between U.S. and international cancer researchers are essential to share knowledge, reduce the cancer burden, and improve global health.

In addition to reducing the devastating human toll of cancer, our Nation's commitment to cancer and biomedical research strengthens our economy, fortifies America's competitive standing in the world in science and technology, and maximizes opportunities for continued major advances against cancer by recruiting, training, and retaining an optimal biomedical research workforce. In fact, according to a 2008 study by Families USA, each dollar of NIH funding

The NIH is comprised of 27 research-focused institutes and centers including the NCI, which is the largest single NIH institute. More than 80% of NIH's budget is distributed in the form of competitive grants that support the research of more than 325, 000 researchers in over 3, 000 laboratories, clinics, universities, small businesses, and private companies in all 50 states and abroad.

The Cancer Research Advocacy Community:

A movement that has served as a catalyst for accelerating progress in cancer research for 40+ years

The cancer research advocacy community has been a critical component in the fight against cancer for decades. For example, in 1971, an influential fundraiser and activist, Mary Lasker, collaborated with Dr. Sidney Farber, a specialist in children's diseases and namesake of the Dana-Farber Institute in Boston, to provide scientific legitimacy to her special cause, conquering cancer through biomedical research.

Today, the entire cancer research advocacy community—cancer survivors and patient advocates, citizen activists, philanthropic organizations, scientific and clinical societies, government, academia, and the pharmaceutical and biotechnology industries—is working collectively to reduce cancer incidence and mortality and advance the cause on all levels. This collection of advocates is the force behind raising funds from the public for meritorious cancer research projects; heightening public awareness of screening and early detection measures, enrollment on clinical trials, education of patients about specific treatment options; providing emotional and financial support to people who have cancer and to their families and caregivers; facilitating innovative collaborations to address key research challenges; sponsoring scientific conferences that spark opportunities for mutually beneficial interactions; lobbying for legislation to increase federal funding for cancer research and to ensure high-quality cancer care; and creating a sense of community towards our common goal: the conquest of the more than 200 different diseases we call cancer.

More specifically, cancer survivors and patient advocates are becoming increasingly involved and influential in the cancer research process and public policy by serving with distinction on advisory boards and committees that oversee the policies and procedures involved in cancer research. These individuals are bringing the patient perspective to NIH's and NCI's overall research program portfolio and are ensuring the continued success of cancer clinical trials by identifying unforeseen risks or barriers to recruiting patients for clinical trials, providing input into the informed consent process, and helping educate potential participants about the importance of standards for biospecimen collection and privacy.

Cancer survivors and patient advocates are identifying innovative ways to support science that oftentimes is proving to be revolutionary in advancing the field and accelerating the development of new treatments. These groups are catalyzing collaborations among researchers, and spurring interest in understanding the complex and interrelated factors associated with all cancers. Many of the new and innovative research models that cancer research advocacy organizations are supporting are ultimately being adopted by the NIH and NCI, which can use their precious resources to propel the research even further ahead.

Laboratory researchers and physician-scientists are recognizing more and more the value that advocates bring to the research process and are reaching out to them as valuable allies in their efforts to understand cancer. The work of cancer survivors and patient advocates in disseminating educational materials to the general public, especially high-risk individuals and the minority and medically underserved, as well as producing survivorship and wellness information and developing patient navigation and outreach strategies, has been pivotal in ensuring mutual understanding between cancer researchers, physician-scientists, and patients. The increasing role of cancer survivors and patient advocates and their respective organizations in the research process itself is also resulting in an increased appreciation for the enormous impact of this disease on those who are diagnosed with cancer and on their caretakers and their loved ones.

In addition to cancer survivors and patient advocates, countless not-for-profit organizations, including scientific societies like the AACR, operate on an international, national, and local level to advance progress against cancer. For example, among other things, the AACR sponsors more than 20 major scientific conferences every year and publishes 7 scientific journals that provide researchers with a roadmap for future research opportunities as well as other vital information that is necessary to translate their discoveries into improved patient care.

While an essential component of cancer research, the funds raised and distributed by patient advocacy organizations and others could never replace those provided by Congress to the NIH and NCI. Therefore, in spite of the incredible supplementary support from the broader cancer research advocacy community, our Nation cannot afford to turn its back on the established leadership of the NIH and NCI in fundamental cancer and biomedical research. With opportunities for major advances in cancer care within our reach, the Nation is being called upon by the advocacy community to address the cancer burden with passion and sustained commitment.

generates more than 2 times as much in state economic output through the "multiplier effect" in the communities where the research is conducted[13].

Today, more than any time in our history, cancer researchers are maximizing the impact of the fundamental discoveries made over the past 40 years and are translating them into improved patient care. This report captures many of the remarkable discoveries that are the direct result of the dedicated work of thousands of researchers working around the country and the world who are poised to exploit the current scientific momentum to create more effective interventions and save more lives from cancer.

Setting the Stage for the Conquest of Cancer

The National Cancer Act of 1971

Historically the United States has repeatedly demonstrated its commitment to the fight against cancer. Our Nation's policymakers' long-standing, bipartisan commitment to reducing the burden of cancer has resulted in countless notable successes and has created an extraordinary foundation of scientific knowledge and an ever-increasing understanding of this devastating disease.

The conquest of cancer became a cornerstone of our Nation's health agenda as far back as 1937, when President Franklin Delano Roosevelt signed the National Cancer Institute Act which established the country's first-ever independent research institute to "provide for, foster, and aid in coordinating research related to cancer."

Twenty-five years later, then President John F. Kennedy declared that Americans would land on the moon before the

December 23, 1971: President Nixon signs the National Cancer Act of 1971, making the conquest of cancer a national priority.

Shortly after beginning my freshman year at Duke University in 2006, I developed intense headaches. I didn't think much of them at first, but tests soon found the cause: chordoma, a very rare cancer that usually starts in the spinal column or skull. Only about 300 people are diagnosed with chordoma each year in the U.S., and when I was diagnosed, there were very few treatment options.

I had surgery to remove the tumor and after I recovered, my mother and I started the Chordoma Foundation in an attempt to accelerate the development of new treatments (see **Sidebar on Cancer Advocacy Community,** p.15). I also began working in the laboratory of Duke oncologist, Michael J. Kelley. At the time, Dr. Kelley was the only federally funded scientist studying chordoma, and the research was challenging. There was no access to tumor samples, and the few researchers studying chordoma were unaware of one another and of other projects and tools.

When my mother and I started the Foundation, there was only one chordoma cell line for researchers to study. Now we have a second, and 3 more are currently being validated at Duke. The Chordoma Foundation has provided the first 2 valid cell lines to more than 40 labs, including many that were not previously studying chordoma. We have also set up a centralized biobank to collect tissue from hospitals across the country and we make it available to researchers who need it.

As critical research tools like these have become available, the number of researchers interested in studying chordoma—and the opportunities for discovery, both in chordoma and other cancers—have dramatically increased. In 2008, for example, several researchers published data indicating that a biological process known as the mTOR pathway is highly active in chordoma. Researchers in Italy are now conducting a clinical trial treating patients with drugs that inhibit this pathway, and they have had some preliminary success: Tumors stopped growing for 6 months, on average, in patients with advanced disease. It is not a cure, but it's definitely a step in the right direction.

In another sign of progress, researchers at the National Cancer Institute collaborating with Dr. Kelley in October 2009 found the cause of familial chordoma: a duplication of the *Brachyury/T* gene. This was the first time that a gene duplication was discovered to cause cancer, and it suggests that duplication of other genes might be a factor in susceptibility to other types of cancer. Further research has found that extra copies of the *Brachyury* gene are also present in many sporadic chordomas—those not linked to a family history.

Since these discoveries, 2 different labs have been able to turn *Brachyury* off in chordoma cells, stopping cell proliferation in laboratory experiments. Now 2 labs are trying to do the same thing in mice. Researchers at the National Cancer Institute have also recently found that *Brachyury* plays an important role in several other types of cancer, so it is possible that figuring out how to target this gene with drugs will have an impact beyond chordoma.

But despite these advances of just the past few years, there are still only 2 chordoma projects underway that are funded by the National Institutes of Health (NIH). As a result, progress isn't being made as fast as it could. More funding from the NIH would certainly help facilitate new discoveries. But beyond providing funding to researchers, the NIH could make a big impact on rare cancers like chordoma by including them in existing programs such as The Cancer Genome Atlas and the newly launched Therapeutics for Rare and Neglected Diseases program. The Cancer Genome Atlas could help identify the molecular pathways driving these diseases, and it could help identify new cancer genes such as *Brachyury* that play a role in multiple types of cancer. And when potential therapeutic targets like *Brachyury* are identified, the Therapeutics for Rare and Neglected Diseases program has the potential to translate these discoveries into drugs suitable for investment by pharmaceutical companies.

When I was diagnosed in 2006, there were only a handful of researchers studying chordoma, and there were no drugs to treat it. Now, thanks to growing awareness, there are about 170 scientists researching the disease around the world, and scientists have found strong evidence suggesting that mTOR inhibitors and other available drugs might successfully manage the disease. We need to continue this trend. If we can extend survival even a few years at a time, then that's a step in the right direction.

end of the decade—and we did. This seemingly impossible achievement, coupled with the success of the polio vaccine and the thought that there could be a viral basis for certain cancers, clearly focused national pride and reinforced the belief that, given the necessary resources, U.S. researchers could accomplish the "impossible" and conquer cancer.

It was in this environment that philanthropist Mary Lasker, Sidney Farber, M.D. from Children's Hospital Boston, and Benno Schmidt, Jr., former Chairman of the Congressionally established National Panel of Consultants on The Conquest of Cancer, led an unprecedented research advocacy effort that inspired President Nixon and Congress to enact the historic legislation that marked a turning point in the Nation's efforts to prevent and cure cancer (see **Cancer Research Advocacy Community Sidebar**, p.15 and meet cancer survivor and cancer research advocate **Josh Sommer**, p.17). The National Cancer Act of 1971 had the bipartisan support of Congressional lawmakers, who recognized the importance of the government's commitment to conquering cancer by advancing cancer research. The Act, which set in motion a coordinated and focused approach to cancer research, was applauded by millions of Americans whose lives would be forever altered by the words, "You have cancer."

President Franklin D. Roosevelt dedicated the new National Institute of Health campus in Bethesda, Maryland, October 30, 1940.

In the period leading up to the passage of the National Cancer Act, the opinion of policymakers was that if something as seemingly impossible as landing on the moon could be accomplished, how much harder could it be to cure cancer? As we now know, curing all cancers would turn out to be harder than anyone could have imagined. In fact, the scientific discoveries that have permitted us to grasp and increasingly understand the extraordinary complexity of cancer were just being uncovered in the early 1970s. Perhaps the most astounding discovery made during these formative years was how "clever" cancer cells are—often defying expectations by changing and adapting to new interventions.

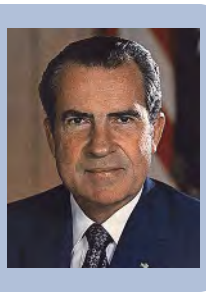
Today, thanks to the fundamental discoveries made possible by our Nation's investment in scientific research, we know that there are more than 200 diseases that we call cancer. We are also now learning how to identify and interpret a cancer cell's unique molecular characteristics. These biological markers, or biomarkers, are making it possible to detect cancer earlier, identify high-risk individuals and populations, and develop more effective and less toxic cancer treatments that work by targeting and blocking the specific proteins, enzymes, and signals that fuel the growth of these different types of cancer cells.

The federal government's support of research has provided our newfound understanding of cancer at the molecular level, which has revolutionized the characterization of cancers, drug development, clinical trials, prevention, and

"That for those who have cancer and who are looking for success in this field, they at least can have the assurance that everything that can be done by government, everything that can be done by voluntary agencies in this great, powerful, rich country, now will be done."

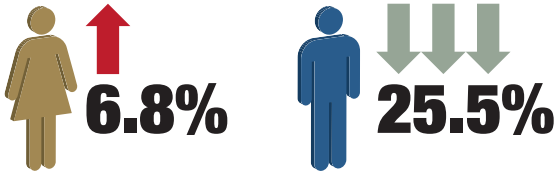
President Richard M. Nixon

Remarks on Signing the National Cancer Act of 1971, December 23, 1971



treatment. Further, the advances made against cancer have had significant implications for the treatment of other costly diseases such as diabetes, heart disease, Alzheimer's, AIDS, rheumatoid arthritis, and macular degeneration. The pages that follow chronicle much of the progress that has been made against cancer.

DEATH RATES FOR LUNG AND BRONCHUS (1990-2006)



EST. 2011 INCIDENCE = **221,130** • DEATHS = **156,940**

Esteemed cancer researchers and AACR Past Presidents prepare to enter the White House for the historic signing of the National Cancer Act into law by President Nixon, December 23, 1971. Pictured, front row, left to right, Drs. Arthur C. Upton, Jacob Furth, James F. Holland, Joseph H. Burchenal, and Sidney Weinhouse.

THE NATIONAL INSTITUTES OF HEALTH ESTIMATED THE 2010 OVERALL ANNUAL COSTS OF CANCER WERE AS FOLLOWS:

TOTAL COST: **$263.8 BILLION**

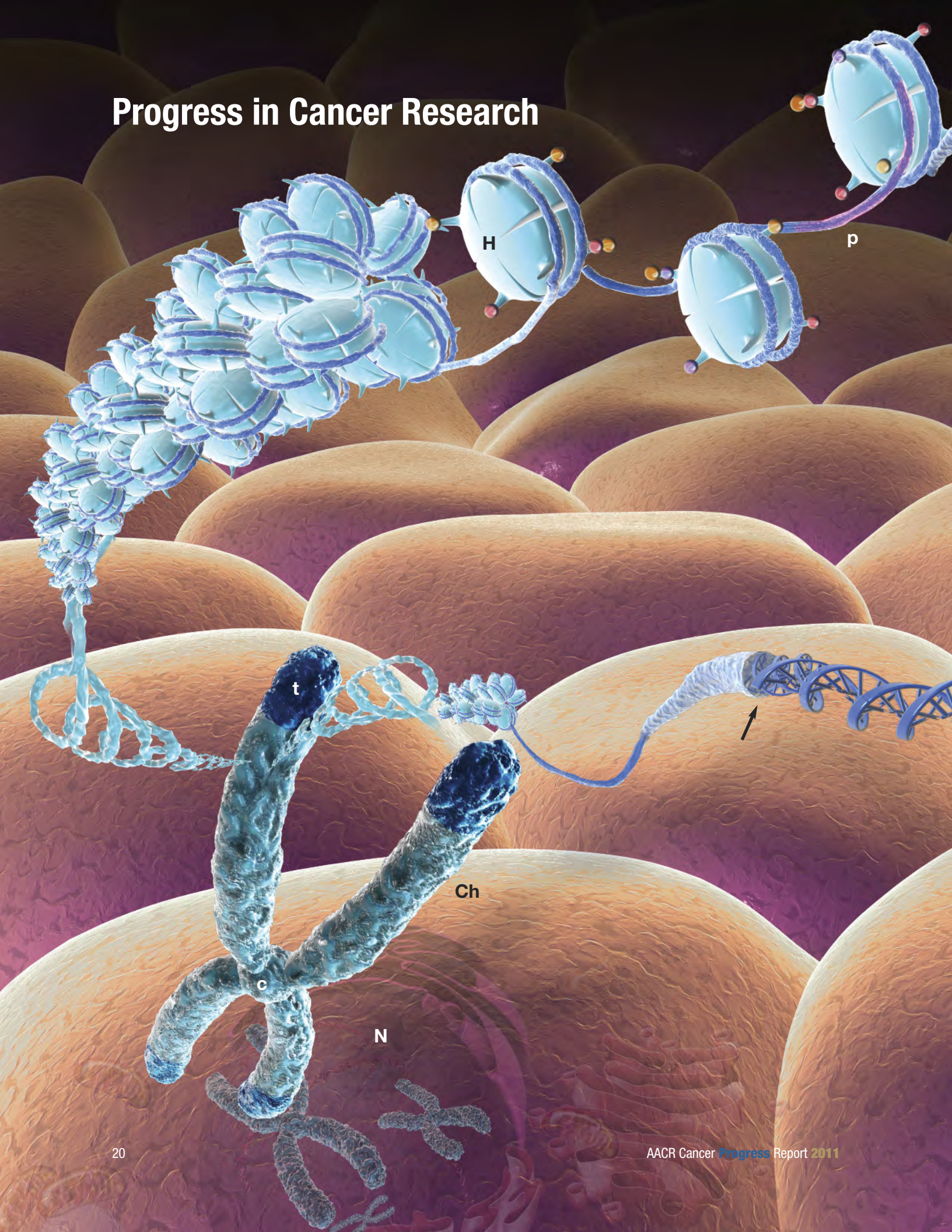
DIRECT MEDICAL COSTS (TOTAL OF ALL HEALTH EXPENDITURES): **$102.8 BILLION**

INDIRECT MORBIDITY COSTS (COST OF LOST PRODUCTIVITY DUE TO ILLNESS): **$20.9 BILLION**

INDIRECT MORTALITY COSTS (COST OF LOST PRODUCTIVITY DUE TO PREMATURE DEATH): **$140.1 BILLION**

SOURCE: ACS

Progress in Cancer Research



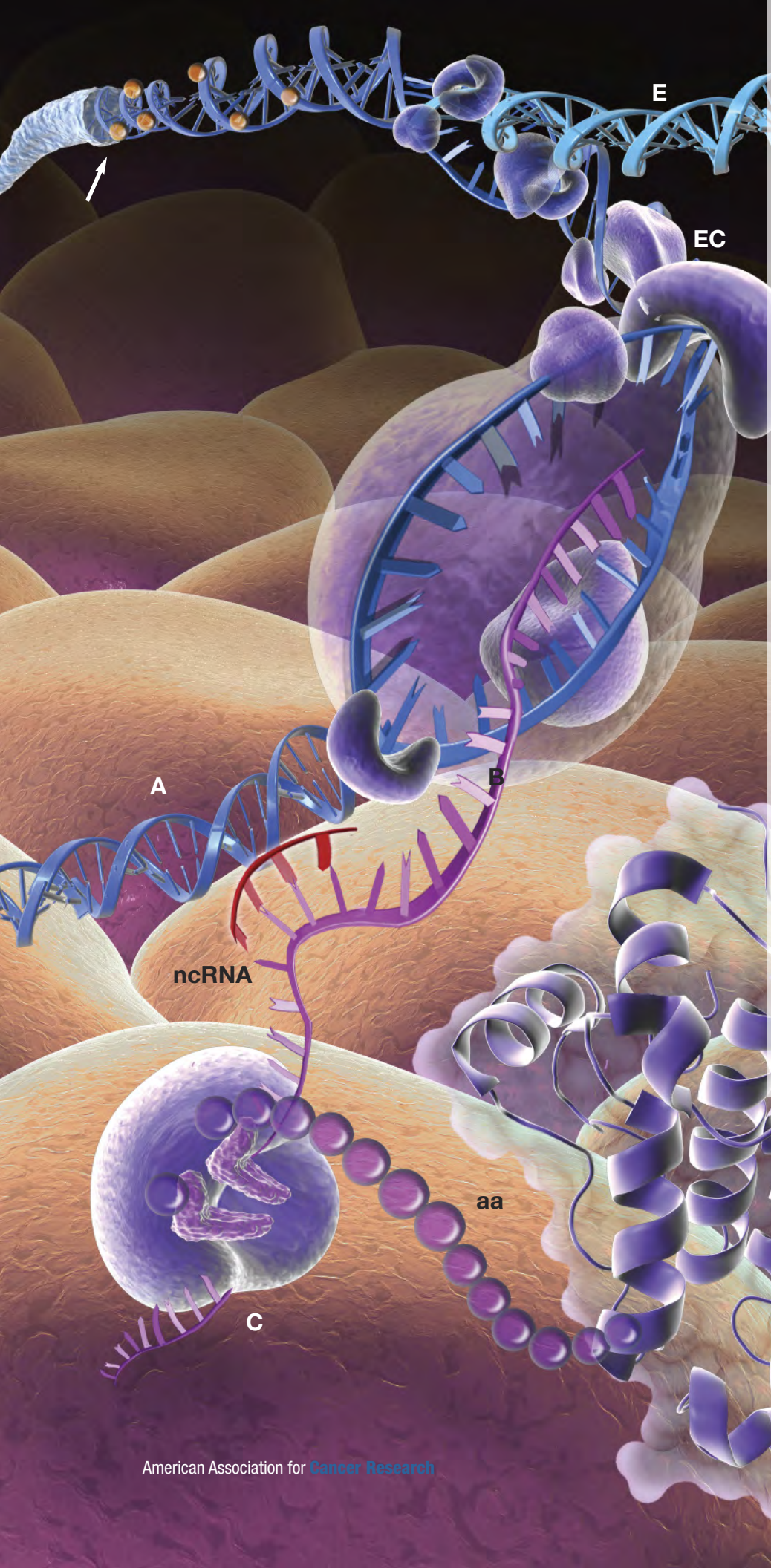


Figure 1: The Basis of Genetics. The entire set of instructions for a cell to function properly is encoded within its DNA (A). This DNA, or deoxyribonucleic acid, is made of chemicals called purines and pyrimidines, known as bases. These bases can be read like the letters A, C, G, T, whose precise order is essential for a cell to function properly. Long strings of these bases then make up pieces of the genome called genes (the DNA between arrows), which are stored in collections called chromosomes (Ch) that are packed within the nucleus or control center of each cell (N). Within each cell over 6 feet of these very thin DNA molecules are packed into the chromosomes using proteins called histones (H). Each chromosome has specific DNA sequences near its center, the centromere (c), and at its ends, the telomeres (t).

Humans have 46 chromosomes within the nucleus of each cell, 23 of which come from your mother and 23 from your father. Changes in the number of chromosomes can result in disease; changes in chromosome structure and integrity lead to several types of cancer, as do exchanges between different chromosomes, called translocations, which can produce new types of proteins that cause cancer, or to loss of proteins that prevent cancer.

Each time a cell divides, all its DNA has to be copied, a process called *replication* (E). Replication occurs during the synthesis or "S" phase of a highly regulated process called the cell cycle, see **Figure 2.** In order for the DNA within each cell to be meaningful, it needs to be translated so that the cell can use it. In fact, the DNA "information", consisting of the sequence of its bases within the genes, is converted twice. First it is *transcribed* into a copy called RNA or ribonucleic acid (B), which begins at specific DNA sequences, called promoters (p). The cell then *translates* the messenger RNA (C) into proteins (D) composed of amino acids (aa), which are used to do the work that the cell needs to perform. Together, replication, transcription and translation are known as the central dogma of biology, and are executed by large collections or complexes of proteins known as enzymes (Ec).

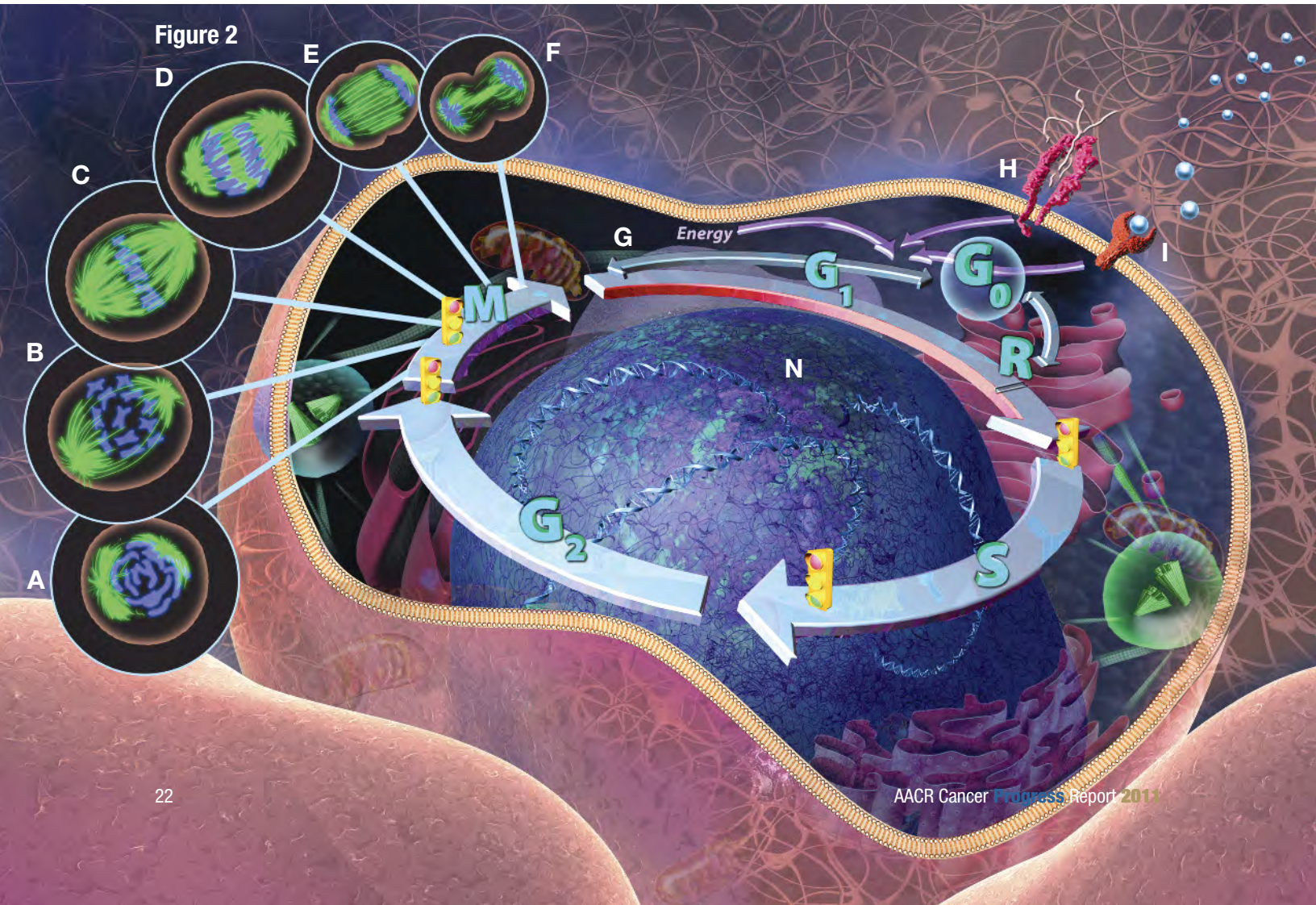
The processes of transcription and translation are controlled at multiple levels. At the most basic level, multiple inputs allow the enzyme complexes themselves to control when, where, and how much of a protein is made. Additionally, chemical modifications of the DNA, the histones, and the production of RNAs that do not make proteins, called non-coding RNAs (ncRNA), allow for fine tuning of these processes. These modifications consist of methylation of the DNA and histones (orange spheres), or phosphorylation and acetylation of the histones (red or purple spheres, respectively). Together, these modifications are known as epigenetics.

Progress in Understanding Cancer

The Genetic Basis of Cancer

One of the greatest advances in cancer research was the discovery that changes, or mutations, in genes can cause cancer. The "genetic code" carried in deoxyribonucleic acid (DNA) units, called bases, is packaged into chromosomes that are passed from parents to offspring (see **Figure 1**, pp.20-21). The entirety of a person's DNA is called a genome. The genetic code within our genome is decoded to produce the various proteins that our cells use to function. In cancer, these chromosomes sometimes break and re-combine; this causes large-scale changes within the genome that can result in the production of abnormal proteins which fuel excessive cell growth, or in the loss of other proteins which usually maintain normal cellular functions. Cancer cells have large numbers of these types of changes.

DNA can also be altered by single mutations in the units that make up DNA**.** Over the years, researchers have identified two key classes of these abnormal cancer genes: oncogenes



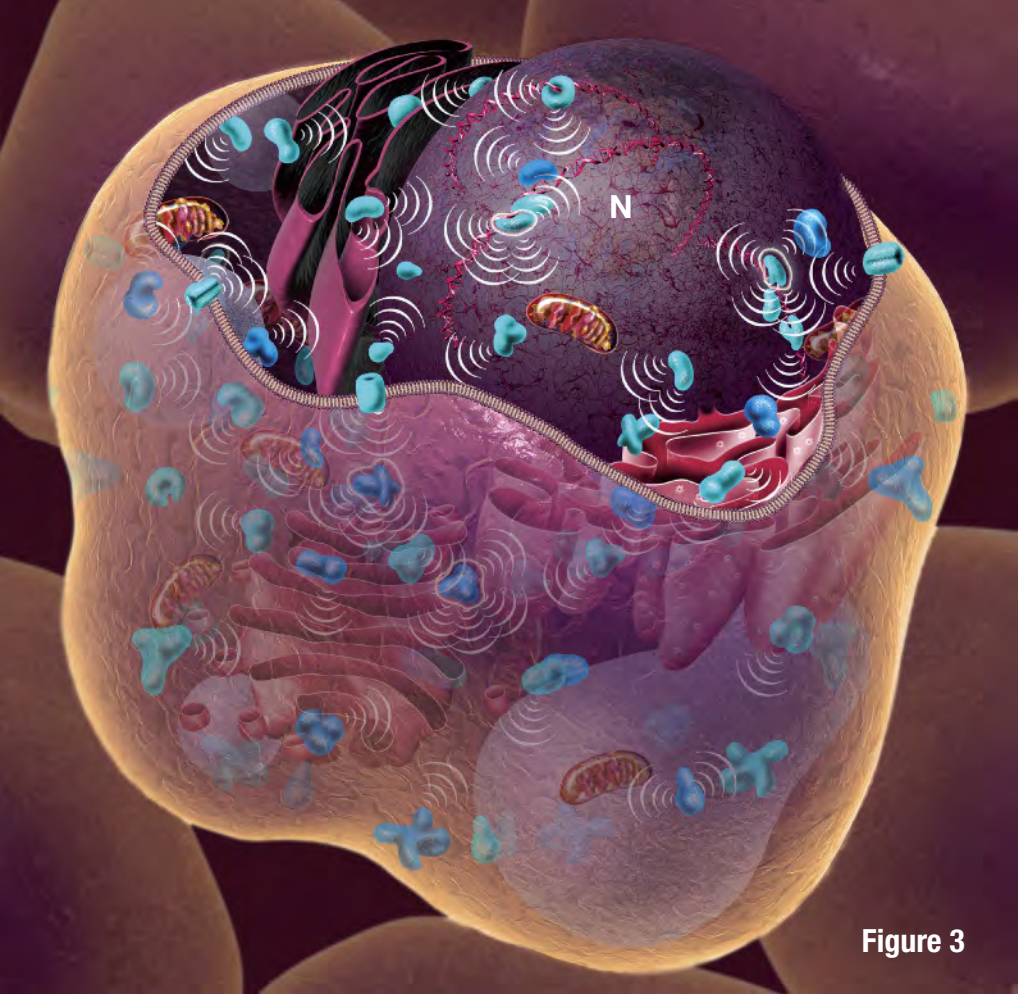


Figure 3: Cell Signaling. Cells communicate with each other through a variety of methods, including hormones, growth factors, elements like calcium, and gases like nitric oxide. These signals originate within a given cell, leave that cell, find, enter, and are interpreted by a different cell. This process of communication is called cell signaling and is highly regulated.

Each type of signal (growth factor, calcium, hormone, etc.) has a specific receiving protein, called a *receptor*, and its own network of other proteins (blue blobs) that aid in the processing of that particular signal. These individual networks are often referred to as pathways. Many networks can interface with other networks, impacting how different signals are interpreted and providing an integrated signal to the cell. Often, signals are relayed from the receiving protein across the network and into the nucleus of the cell (N), where changes in gene activity (red strands) and ultimately cell behavior occur as a result.

Figure 2: The Cell Cycle. The cell cycle functions like a computer to govern the process leading to cell division, processing a multitude of inputs from both inside and outside of the cell and synthesizing that into one of two choices for the cell: proliferate or settle down, also known as quiescence. Within the quiescent state, also known as Gap 0 or G_0 (G_0 circle), there exist at least two options: remain quiescent, but capable of re-entering the cell cycle (arrows to/from G_0 to G_1); or terminally differentiate into a more specialized cell that can no longer re-enter the cell cycle, called post-mitotic.

The various inputs that are processed by the cell cycle include, but are not limited to: the energy state of the cell (G), including nutrient and oxygen levels; the presence of stimulatory growth factors (I); and the status of the microenvironment (H). The balance of these factors ultimately determines if a cell will enter the cell cycle to make more copies of itself or enter the quiescent state.

The cell is only sensitive to these inputs during a particular period within the Gap 1, or G_1 phase (G_1 arrow), of the cell cycle (red portion of G_1 arrow), leading up to a major checkpoint called the restriction point (R), which maintains the fidelity of the cell cycle. Prior to the restriction point, the cell can transit between quiescence and the cell cycle; however, once the restriction point is passed, the cell cycle will proceed and the cell will divide, making new cells.

The actual work performed during the cell cycle is done by a large family of proteins called cyclin-dependent kinases (cdks), which are controlled by a number of inputs including a family of cyclin-dependent kinase inhibitors (not shown). These enzymes are in turn regulated by a central controller, the tumor suppressor known as the retinoblastoma protein or Rb. The activity of Rb controls transit through the restriction point, and Rb must be inactivated in order for the cell cycle to progress. Many oncoproteins, including those of viral origin like HPV's E7, inactivate Rb, which is inactivated in many cancers, allowing for uncontrolled progression of the cell cycle.

In addition to the restriction point, the cell cycle contains at least four main *checkpoints* (stoplights), which function to ensure that the previous phase of the cell cycle was completed without errors prior to moving to the next phase. Therefore, these checkpoints can also function as tumor suppressors. During S phase (S arrow), families of proteins known as DNA damage response proteins inspect the newly copied DNA for errors, and repair enzymes correct any found. These errors can come from the process of DNA replication itself or from various chemicals, radiation or other DNA toxins. DNA damage responders like BRCA1 and 2, the RAD family of proteins, and others are often non-functional in many cancers, allowing the cell cycle to proceed despite errors in the DNA. As these errors accumulate within a precancerous cell, they often confer a competitive advantage to the cell allowing it to operate and multiply independently of the checkpoints in the cell cycle, ultimately leading to cancer.

Cell division itself occurs by a process called *mitosis*, (M phase; see M arrow), which is a coordinated effort between the DNA (blue), the organelles of the cell, and the cell cytoskeleton (green). Mitosis consists of several steps: prophase, metaphase, anaphase, and telophase; the period between cell divisions is known as interphase. During prophase (A), the DNA condenses forming chromosomes visible under the microscope. These chromosomes then attach to the cytoskeleton and begin to align in the center of the cell during prometaphase (B) and are completely aligned during metaphase (C). The cytoskeleton then moves the two copies of each chromosome, formed during the S phase replication process, towards opposite ends of the cell during anaphase (D). Once the chromosomes have arrived at opposite ends, the remaining contents of the cell are divided and new cell membranes and cytoskeletons are formed during telophase (E). During the process of cytokinesis (E and F), the dividing cell pinches apart into two daughter cells (F).

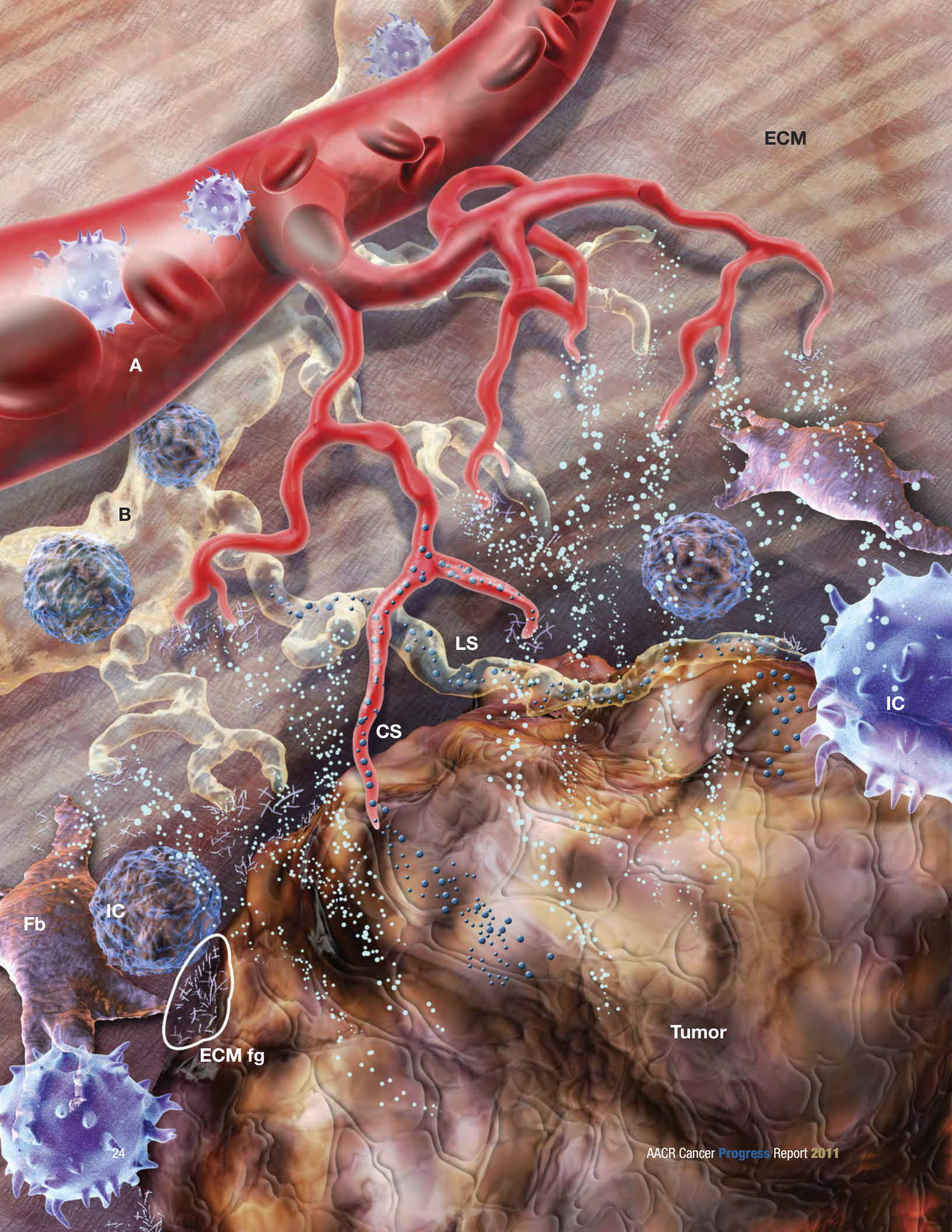

ECM
A
B
LS
CS
IC
IC
Fb
ECM fg
Tumor

Figure 4: Angiogenesis and Lymphangiogenesis. As a tumor grows, it reaches a critical size where it needs more nutrients to continue its rapid expansion. At this point, the tumor begins to secrete factors (small blue bubbles) that will attract both new blood (A) and lymphatic (B) vessels, known as angiogenesis and lymphangiogenesis, respectively. Here, a number of capillary (CS) and lymphatic (LS) sprouts are approaching the tumor in response to these factors. One such growth factor is vascular endothelial growth factor (VEGF), which is blocked by the drug bevacizumab (Avastin, **Table 3**, p.42). A growing body of research has demonstrated that the tumor's environment is also critical for this process. Immune cells (IC), local fibroblasts (Fb), the extracellular matrix (ECM), and fragments of the ECM (ECM fg), released by degradation, play an active role in angiogenesis and lymphangiogenesis. Bevacizumab and other drugs (**Table 1**, p 13.) that target these processes have been successful in treating a variety of cancers.

and tumor suppressor genes. By directing genes to produce aberrant proteins that permit cancer cells to ignore normal growth regulatory signals, oncogenes can drive the initiation and progression of cancer. Tumor suppressor genes encode proteins that normally stop the emergence of cancer by repairing damaged DNA and regulating the multiplication of cells (see **Figure 2**, p.22). Mutations in tumor suppressor genes block DNA repair and allow cancer cells to ignore the signals that control normal cell growth and proliferation. Accumulating DNA mutations enables the cancer cells to continually adapt and evade treatment.

To date, over 290 cancer genes have been discovered, and the list continues to grow as advanced technologies facilitate the generation of complete sequences of DNA from cancer cells. A significant number of these mutations code for abnormal proteins, called kinases, which are key components of the numerous signaling networks in cells that drive a large number of cellular functions (see **Figure 3**, p.23). Kinases turn signaling networks on and off; however, within cancer cells, they have become mutated in ways that often keep the networks permanently "on," thus permitting the cancer cells to grow uncontrollably.

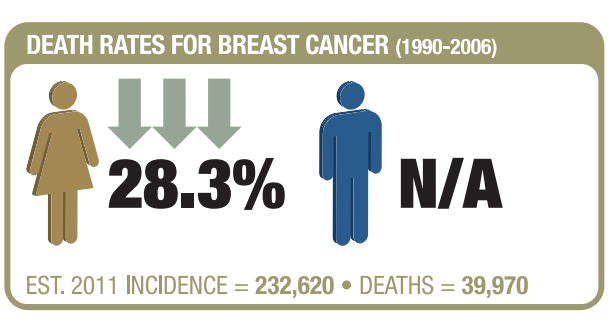
The correlation of genetic mutations with changes in cell behavior, especially in cancer, was the impetus for the Human Genome Project, the international effort spearheaded by the NIH to sequence the 3 billion bases in the human genome. Completed in 2003, the Human Genome Project provided researchers with the complete normal sequence of DNA in the human body, which could then be used as a reference to identify genetic changes in cancer and other diseases. Capitalizing on the important information provided in this reference genome, the NCI and the National Human Genome Research Institute launched The Cancer Genome Atlas (TCGA) in 2006. The goal of TCGA is to identify all of the relevant genomic changes in most types of cancer by comparing the DNA in a patient's normal tissue with that of the DNA in the tumor.

Beyond our knowledge of the changes in chromosomes and specific mutations in DNA, through research we have learned that DNA can be further altered by the addition of specific chemical entities to it, or in the way it is "packaged" into chromosomes, known as epigenetics (see **Figure 1**, pp.20-21). Research is demonstrating that epigenetic changes, which can occur in the absence of specific DNA mutations, are critically important to understanding how cancer originates and evolves. Like the Human Genome Project, the International Human Epigenome Consortium is currently working to define the normal reference epigenome.

Decades of research to understand how changes in the genome cause cancer have produced unparalleled opportunities for future progress in diagnosing, treating, and preventing this complex disease. Continued progress in cancer genomics and epigenomics will stand as powerful strategies to drive molecularly based cancer science and medicine in the future and speed the delivery of its benefits to patients.

Beyond Genetics: The Cancer Cell's Environment

In the decades since the passage of the National Cancer Act, cancer researchers have continued to accumulate knowledge that is enabling our understanding of cancer at all levels. We now recognize that the altered genomes of cancer cells can have a profound effect on the development



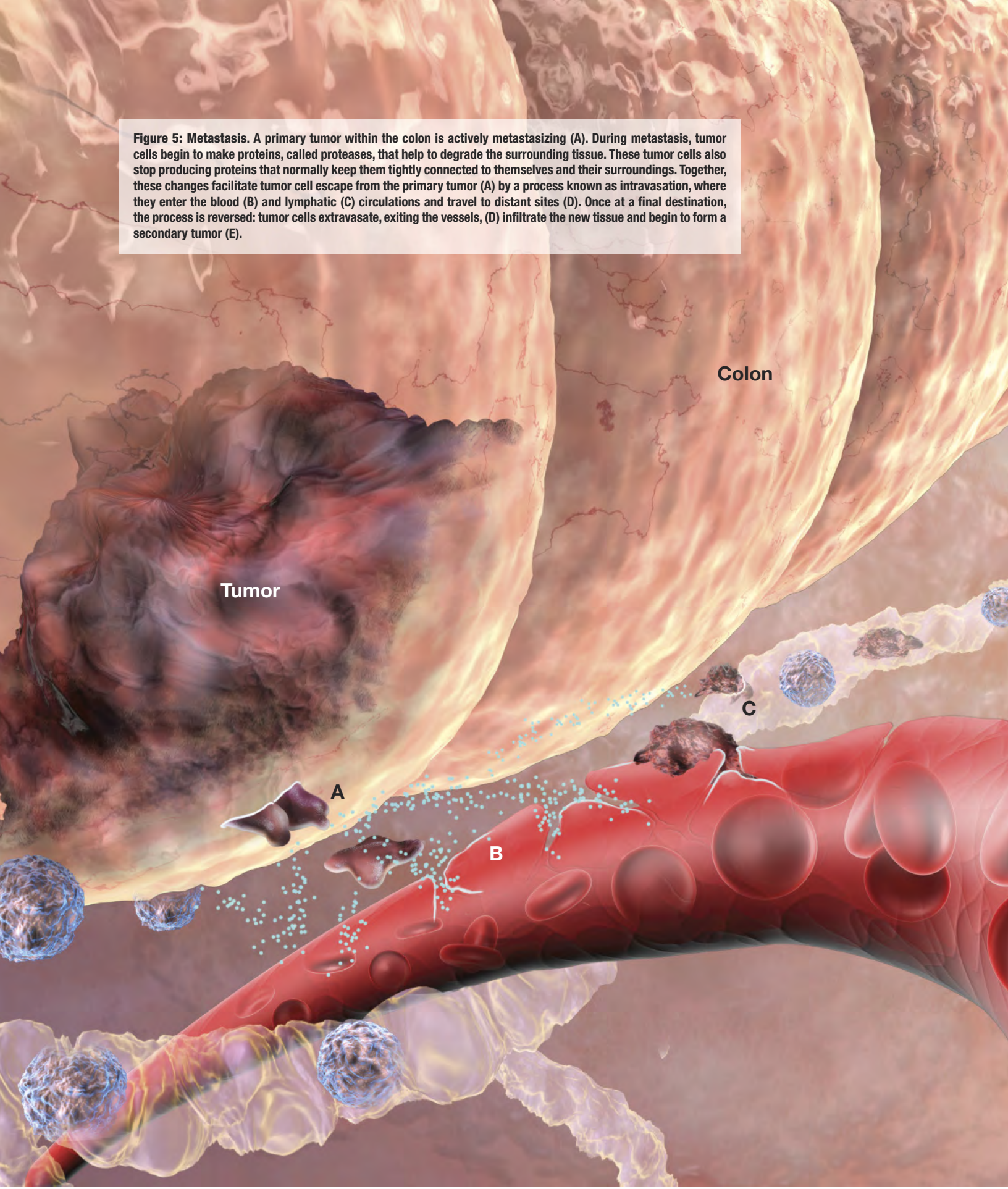
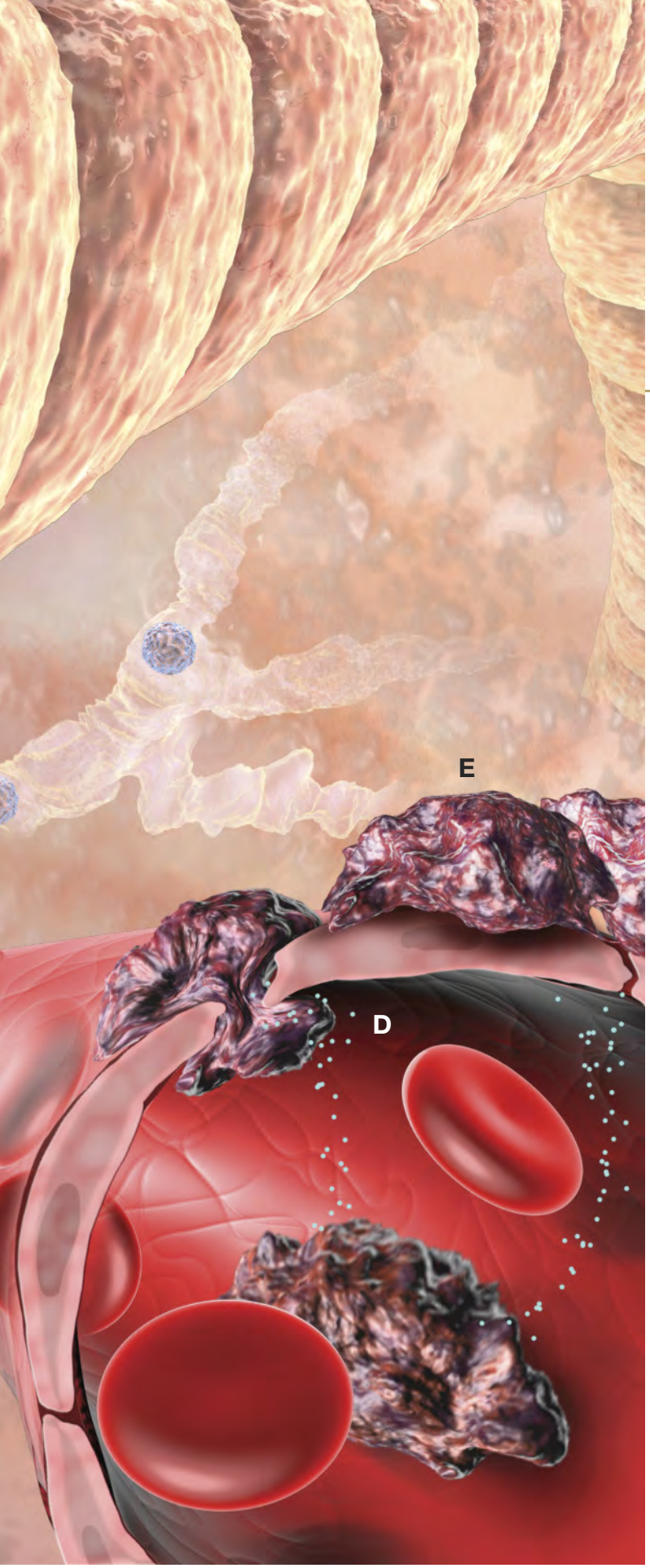


Figure 5: Metastasis. A primary tumor within the colon is actively metastasizing (A). During metastasis, tumor cells begin to make proteins, called proteases, that help to degrade the surrounding tissue. These tumor cells also stop producing proteins that normally keep them tightly connected to themselves and their surroundings. Together, these changes facilitate tumor cell escape from the primary tumor (A) by a process known as intravasation, where they enter the blood (B) and lymphatic (C) circulations and travel to distant sites (D). Once at a final destination, the process is reversed: tumor cells extravasate, exiting the vessels, (D) infiltrate the new tissue and begin to form a secondary tumor (E).



The Impact of Cancer Metastasis

Metastasis is the spread of cancer from a primary tumor to other areas of the body where the cancer cells establish new tumors (see **Figure 5**, p.26). It is this most lethal attribute of cancer cells that is responsible for more than 90% of the morbidity and mortality associated with cancer. Therefore, studying the fundamental properties of metastasis is essential to conquering cancer. Through research, we will learn how to predict who will develop metastatic cancer. We also need to identify important targets for the development of new therapies that will prevent or treat metastasis.

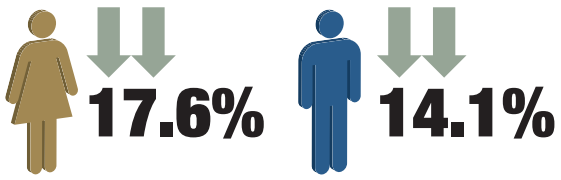
Already we have learned a great deal about this deadly process, some of which explains why metastatic disease is so difficult to treat. For example, virtually every step of the metastatic process can be achieved through multiple different means, giving the cancer cells many opportunities to metastasize. This also means that blocking only one pathway therapeutically will not be sufficient.

We also understand that metastasis is a distinct property of cancer cells, not a property of all cells. Furthermore, not all cancer cells within a metastatic tumor are capable of metastasizing, and not all cancers become metastatic. New research has revealed that there is a genetic basis for susceptibility or resistance to metastasis. These findings create new avenues for effective therapies.

Another critical finding is that cancer cells can travel to other parts of the body, and then lie dormant in a new location for years, only to become active again later in life. A greater understanding of the factors that contribute to tumor cell dormancy could lead to the development of new therapies that have the potential to prevent these dormant cells from reawakening.

Metastatic disease is a dire situation that requires an immediate and complete therapeutic response in order to prevent almost certain death. Only with continued research into this complex process can we hope to make significant progress against cancer and save lives.

DEATH RATES FOR BRAIN AND NERVOUS SYSTEM (1990-2006)



EST. 2011 INCIDENCE = **22,340** • DEATHS = **13,110**

Figure 6: The Role of the Immune System in Cancer. Within the epithelial lining of an organ, genetic errors can occur generating pre-neoplastic epithelium, circled in white, which can give rise to a tumor (A). During this process, the immune cells (colored spheres in B, C, and D) may attack certain cells within the tumor (B, purple color), while leaving others alone (B, brown color). In some cases, the immune response is effective and the tumor is completely eliminated (Elimination). If the immune response is unable to clear all of the tumor cells (Equilibrium), the cells that escape elimination (C, brown cells) will go on to form a larger tumor (D, Escape). Here the immune cells [CD4-T, CD8-T, NK-T(1), NK, and macrophages (Mac)] enter into equilibrium with the tumor, such that the tumor does not get any larger, but the immune cells can not eliminate it (C). Ultimately, this state of equilibrium will progress to tumor escape and metastasis (Escape, red tumor, and D, respectively). The immune cells are inhibited by a number of tumor and host factors, including other cells of the immune system, such as regulatory T cells (T-reg), myeloid derived suppressor cells (MDSC), NK-T2 cells, and mast cells. Fundamental research has provided a deeper understanding of the individual immune cells involved at each stage, allowing new immune therapies to be developed. In the last 2 years, 2 such drugs – one for prostate cancer (sipuleucel-T) and a second for melanoma (ipilimumab) — received FDA approval; see cancer survivor **Andrew Messinger, p. 57.** Many other immune therapies are undergoing active clinical investigation with positive early results; see cancer survivor **Roslyn Meyer, p. 59.**

and spread of cancer by changing the environment that surrounds the cancer cells, known as the tumor microenvironment.

Examples of factors that make up the tumor microenvironment are: the type, quantity, and modification of the proteins outside the cell that provide structure and function, known as the extracellular matrix; the ability to create new blood and lymphatic vessels (angiogenesis and lymphangiogenesis, respectively); hormones; nutrients; and the immune system. Because of progress in cancer research, we have discovered that the tumor microenvironment profoundly affects the ability of cancers to grow and spread, or metastasize, to other parts of the body.

Tumor-directed angiogenesis and lymphangiogenesis enable cancers to grow uncontrollably (see **Figure 4**, p.24) and provide a mechanism for tumor cells to escape into the circulation and potentially infiltrate other organs. Adding to the complexity of metastasis, the extracellular matrix can also be modified by cancer cells to specifically alter these processes.

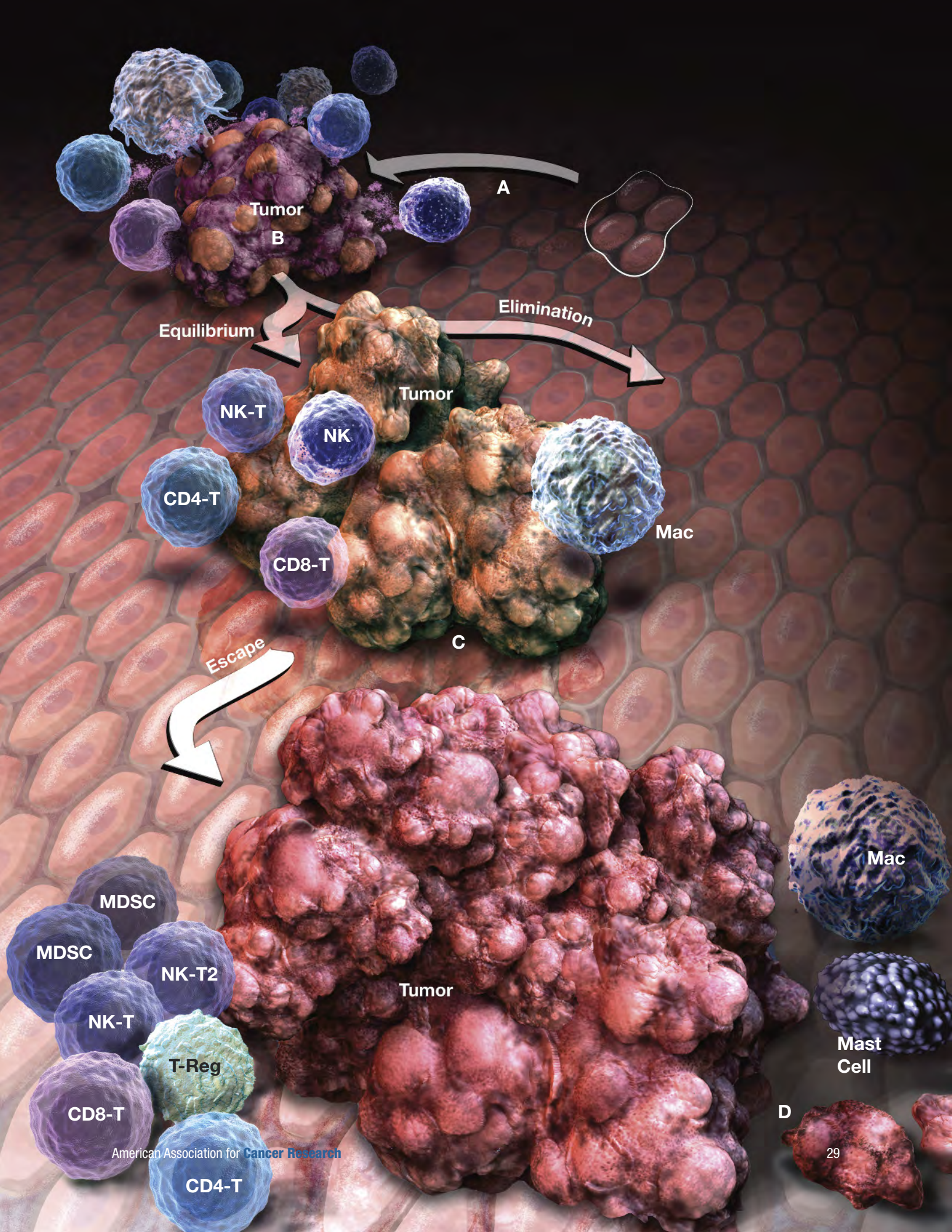
Cancer metastasis continues to take the lives of too many patients. Increasing our understanding of this process and our ability to control it are major challenges in cancer research today. Many questions remain about how metastatic tumors differ from the primary tumor and about what biological processes are required for metastasis to occur. Cancer metastasis is an area of intense investigation and will be for the foreseeable future (see **Figure 5**, p. 26 and **Metastasis Sidebar**, p. 27).

Finally, progress in our understanding of the immune system and how it contributes to the development and evolution of cancer is producing new therapies. We are just now beginning to understand that inflammation, resulting from a variety of causes, plays a central role in tumor formation and progression (see **Figure 6**, p. 29). Further, it has recently been discovered that tumors block their own destruction by the immune system through the inactivation of immune cells. This important finding has opened the pathway for the development of novel therapeutics and therapeutic strategies.

"Our intensified cancer research effort was born of public concern about the problems of cancer, which takes many forms, and it has our continuing support and commitment."

President Gerald R. Ford

Message to Congress When Transmitting Report and Plan for the National Cancer Program, April 5, 1976


A
Tumor
B
Equilibrium
Elimination
Tumor
NK-T
NK
CD4-T
Mac
CD8-T
C
Escape
Mac
MDSC
MDSC
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Estimated Percentage of Cancer Deaths Attributable to Established Risk Factors

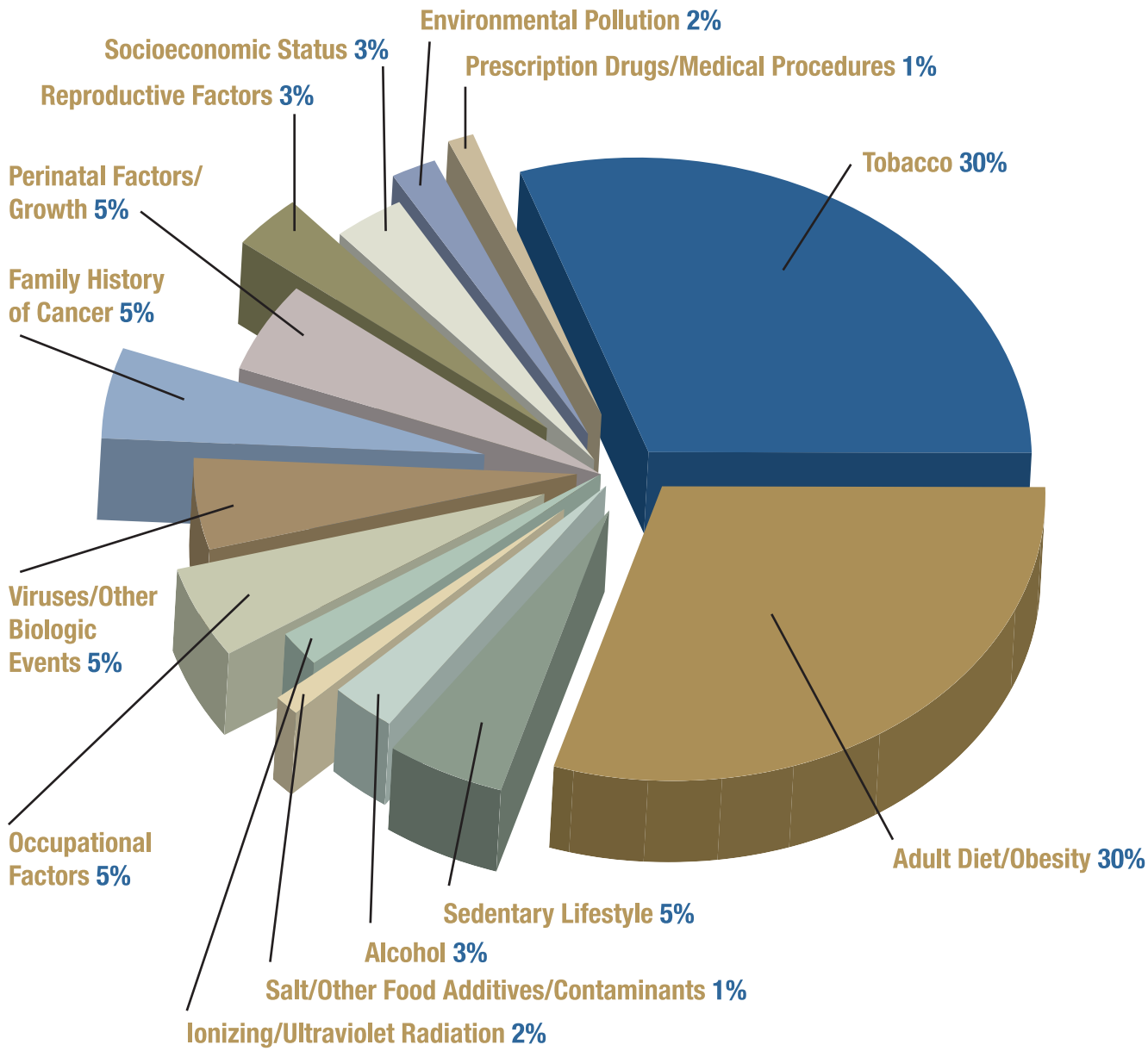


Figure 7: Given that the majority of cancer deaths are due to preventable risks such as tobacco, obesity/energy balance, alcohol consumption, and infectious agents, approximately 50% of all cancers and cancer deaths could be prevented by modifying personal behaviors. See also, **Behavioral Research, Energy Balance, Health Behaviors Sidebars,** and **Infectious Agents,** pp. 32, 36, 33, 34, respectively.

In short, the Nation's investments in cancer research over the last 40 years have produced remarkable progress in understanding the causes of cancer initiation and progression at the molecular, cellular, and tissue levels. This new knowledge is a result of an ever-accelerating pace of discovery, fueled in large part by the availability of exciting new technologies. As a result, we now know that the complexity of cancer exists at every level: from populations, to individuals, to specific cancers, and to the very genes that drive these cancers.

Uncovering the mysteries of cancer requires the collaboration of researchers from a wide range of disciplines and the convergence of new advanced technologies and computing with the molecular sciences. Clearly the promise of future cancer cures and prevention will be fulfilled in this unprecedented era of molecularly based medicine.

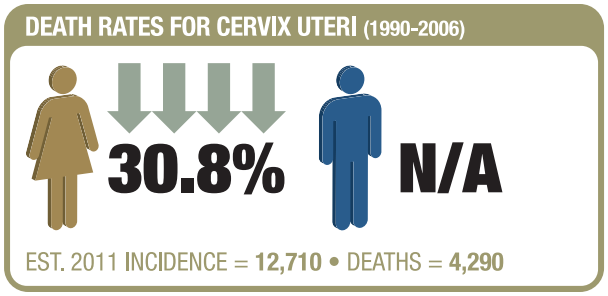
Setting the Standard of Care

Our more complete understanding of the biology of cancer is moving cancer research in exciting new directions. Continued research is now yielding an unprecedented insights into the biology of cancer at the molecular level, and this new knowledge is beginning to transform the current standard of care from a one-size-fits-all approach to personalized cancer care (see, **Personalized Cancer Medicine**, p. 47). However, before discussing the advances that will revolutionize the standard of care in the near future, it is important to cite the many discoveries that have established our current standard of care. We would not be on our current path were it not for the extraordinary medical, scientific, and technological advances that have given us the tools we now use to prevent, detect, diagnose, and treat cancer. Collectively, these advances have helped and continue to define the current standard of care and have saved millions of lives in the U.S. and throughout the world.

Advances in Cancer Prevention

An important area of cancer research includes understanding the causes of cancer and developing the means to detect it and intervene earlier in its progression; or to prevent the onset of cancer altogether. Tremendous progress in cancer prevention has been made through the integration of various research disciplines and technologies, including biochemistry, cell biology, imaging, molecular biology, toxicology, biostatistics, and epidemiology. Some of the greatest reductions in cancer mortality have resulted from the implementation of public health measures and improvements in screening practices that are based on our knowledge of the causes of cancer.

When a family member or friend develops cancer, many people often ponder why. All too often, there is no easy answer because the variables are too numerous and complex. Researchers are beginning to understand some of the risk factors and root causes for certain types of cancer. For example, tobacco use, radiation exposure, hormones, environmental and occupational carcinogens, and infectious agents play a major role in causing cancer (see **Figure 7**, p. 30). Although they are incompletely understood at this time, factors such as diet, lifestyle, and other medical conditions can modify a person's cancer risk (see **Behavioral Research Sidebar**, p. 32).



Behavioral Research and Cancer Control

Advances in identifying what causes cancer have enabled behavioral researchers to bring forward a spectrum of approaches to capitalize on this knowledge. Their goals are to implement behavior change that will reduce cancer incidence and mortality, and improve the quality of life for cancer survivors.

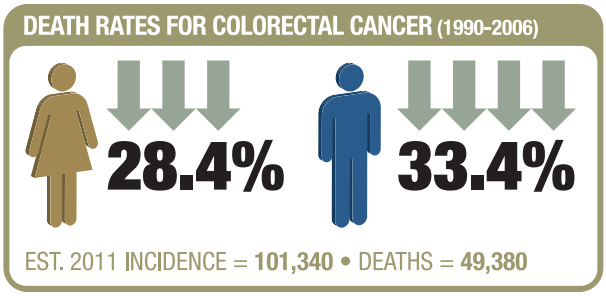
Behavioral research encompasses both qualitative (interviews, focus groups, observation) and quantitative (measurement of attitudes, knowledge, cancer worry or concerns) approaches, which range from describing behavioral patterns to testing strategies that can lead to cost-effective interventions. Behavioral researchers make important inferences from studies involving a few people to studies of entire communities. These inferences enable the testing of appropriately targeted behavioral and educational interventions or policy changes.

The role of behavioral research in reducing tobacco use cannot be overestimated. Reduction of tobacco smoking in the U.S. has benefited from behavioral science findings, particularly at the individual level where a model 4-stage model facilitates interventions for smokers to successfully change their behavior and quit smoking. Also, educational programs, strategies that utilize networks of family and community, nicotine replacement therapy, and policy changes, such as increasing taxes on tobacco products, banning tobacco use in public spaces, and restrictions on tobacco product marketing and advertising, have all been successful in reducing the number of tobacco users in America.

Behavioral research has also helped improve early detection of cancer through the identification of barriers, motivators, and means to increase adherence. For example, increased education and awareness have contributed to increased rates of mammography. In addition, the role of the health care provider in recommending colon cancer screening has been a crucial motivator.

With the introduction in the mid-1990s of cancer genetic testing for susceptibility to breast and colorectal cancers, behavioral researchers have had an important opportunity to study the diffusion of new discoveries and use new technologies to educate cancer patients, family members, and the population at large about risk and lifestyle factors associated with cancer. Key insights have led to development of novel educational programs, genetic counseling services, and the use of genetic test results, as well as policy innovations such as the Genetic Information Nondiscrimination Act.

Since many behaviors are associated with an increased risk of cancer, behavior modification stands to make a significant impact on the reduction of cancer. Continued research in how to maximize behavior modification is an essential component of our cancer prevention efforts.



Tobacco Use and Cancer

The causal relationship between cigarette smoking and lung cancer was first brought to the public's attention in 1964 by the U.S. Surgeon General's Report on Smoking and Health. The Report marked the beginning of major U.S. policy changes, media campaigns, and other measures to combat cigarette smoking, all of which have helped to reduce the percentage of Americans who smoke to about 20% of the population, down from 42% in 1965[4,5].

Since that landmark Report, research has shown that tobacco use is a cause of 18 different cancers[6], including lung, head and neck, stomach, pancreas, and cervical cancers, among others, and accounts for 30% of all cancer deaths in the U.S.[1] A substantial evidence base also proves that exposure to secondhand smoke, or environmental tobacco smoke, also causes cancer, a finding that has led to important policies restricting smoking in public places. In recent decades, there has been a steady decline in lung cancer death rates among men, which is directly attributable to the decrease in smoking prevalence. This success is representative of how scientific progress can inform public policy and educational efforts to measurably reduce cancer rates.

The Surgeon General's 31st report on tobacco, released in 2010, concludes that there is no safe level of exposure to tobacco smoke. Yet, every day 4,000 American youths smoke their first cigarette[14], and 1,000 join the 71 million Americans, aged 12 and older, who regularly use tobacco[15]. Clearly, countless lives can be saved in the future through continued research to develop and implement effective tobacco control strategies.

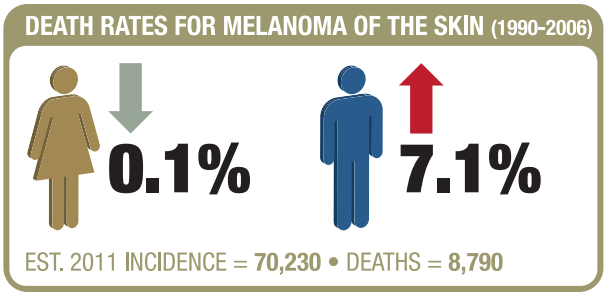
Exposure to Radiation and Environmental and Occupational Toxins and Cancer

Epidemiological research has determined that even low levels of radiation exposure increase cancer risk, and that efforts to limit diagnostic X-ray exposure should be made.

Likewise, excessive exposure to ultraviolet light (UV), a form of radiation, is a risk factor for skin cancer, particularly the most lethal form, melanoma. New standards for sunscreen, increased sun protection, and decreased UV exposure, including avoiding the use of tanning beds, should greatly reduce melanoma and other skin cancers.

Exposure to the naturally occurring radioactive gas, radon, causes between 15,000 and 22,000 lung cancer deaths a year, making it the second leading cause of lung cancer after smoking[16]. This discovery has led to policies for reducing exposure through home and business inspections, and the containment or elimination of the source when possible. Increased awareness along with these mitigation strategies should greatly reduce the incidence of lung cancer caused by these exposures.

The role of environmental and workplace exposures in cancer and other health outcomes has been an important area of epidemiologic and toxicologic research. Agents such as asbestos and the related volcanic rock, erionite, cause an aggressive form of cancer, called mesothelioma, that is difficult to treat. Chemicals like arsenic, aflatoxin, and pesticides, particularly dichlorodiphenyltrichloroethane (DDT), are also associated with an increased risk of a variety of cancers[17]. Our knowledge of their roles in causing cancer has paved the way for important preventive interventions and public policy. Our understanding of how overall exposure, length of exposure, and exposures to multiple toxins contributes to the formation of cancer is still incomplete and requires further study.



Health Behaviors in Cancer Risk and Prevention

In parallel with the many advances in cancer research at the cellular and molecular level, there has been tremendous progress in identifying health behaviors that can affect cancer risk.

A major challenge has been that risk factors for the 200 different types of cancer can differ substantially. For example, some cancers are predominantly dependent on hormonal factors, such as breast, endometrial, or prostate cancer, while others are strongly influenced by dietary components, such as tumors of the gastrointestinal tract. Tobacco smoking is a nearly universal villain, increasing the risk of developing cancer at no less than 18 different tumor sites and accounting for 30% of all cancer cases and deaths in the U.S.

Based on the epidemiologic research to date, it is conservatively estimated that 50% of cancers would be preventable by health behavioral changes. This number gives us hope that cancer prevention measures can make a substantial impact on the lives of millions of Americans, while at the same time save billions in health care dollars.

A major achievement in cancer prevention has been the 2007 World Cancer Research Fund report, entitled "Food, Nutrition, Physical Activity and the Prevention of Cancer – A Global Perspective", summarizing four decades of epidemiologic research on this topic. The 7,000 international research studies draw a clear picture of where dietary changes can be successful and where more work is needed. Avoiding red meat, particularly well-cooked red meat, reduces colon cancer risk, while fruits and vegetables appear generally beneficial with strong risk reductions for lung and gastric cancer.

If diet can have such a large effect on cancer risk, the question remains whether we will be able to prevent cancer by taking vitamin pills. Large-scale prevention trials enrolled thousands of participants to determine if beta-carotene could prevent lung cancer. The results showed not only no benefit, but actual harm. Similar trials are underway to determine if other molecules that are present in fruits and vegetables can prevent cancer.

Another important area of research is the role of vitamin D in colon cancer prevention. Studies have reported that higher vitamin D levels in the blood correspond to reduced risks and better survival; however, vitamin D is also produced in the skin and is linked to physical activity, which complicates analysis of its efficacy. Several NIH-funded trials using vitamin D supplements are underway, and cancer researchers are anticipating the official reports of these studies.

Yet another potential anti-cancer pill comes from a different direction, the non-steroidal anti-inflammatory drugs (NSAIDs). Inflammation fosters the growth of tumors in both humans and animals, and epidemiologic studies in the 1980s reported decreased risks of colorectal cancer among regular aspirin users. In 2003, the first clinical trials reported success in the reduction of colorectal polyps among those taking NSAIDs. Recently, analyses of several large clinical trials showed that more than 5 years of a small dose of aspirin resulted in a 40% reduction in colorectal cancer mortality, but also a significant reduction in the overall cancer mortality.

We do not have a "wonder pill" to prevent cancer and, because of the complexity of cancer, it is unlikely that any one chemopreventive agent is going to offer the desired results. The benefits among women are not clear, and aspirin and other drugs can have side effects. Today's research focuses on identifying genetic factors that predispose individuals to these and other side effects – with the hope that we will be able to harness the potential of NSAIDs and other chemopreventive agents and offer personalized cancer prevention to high-risk populations (see **Molecularly Based Prevention**, p. 65).

We now know that what individuals do on a daily basis can help reduce their cancer risk. Our tools for measuring genetic risk factors, as well as lifestyle and health behaviors, have improved significantly, providing great potential for fruitful research that will close the numerous gaps in our knowledge. Cancer prevention research is a critical component of our goal to conquer cancer, and there is much optimism that success in this area will reduce the burden of cancer to society.

Conquering Certain Cancers by Eliminating Infectious Agents

When the Pap test for cervical cancer was introduced in the U.S. in the early 1940s, it marked the first time that physicians had a way to test for early cellular changes that could go on to become cancer, providing an opportunity to remove precancerous tissue before it became cancer and spread to other organs. It also marked the first time that a test was directly responsible for reducing cancer deaths.

Our success in reducing cervical cancer incidence and mortality was just the beginning. The scientific journey that broke open a new approach to cervical cancer prevention started in 1976, when it was first hypothesized that human papillomavirus (HPV) might play an important role in the development of cancer. Researchers pursued this theory, eventually identifying the presence of HPV in cervical cancer. We now know that persistent infections with high-risk HPVs are the primary cause of cervical cancer, and up to 70% of cervical cancers worldwide are caused by 2 high-risk strains alone, HPV types 16 and 18. HPV infections can also cause cancers of the anus, vulva, vagina, penis, and oropharynx.

Determining which HPV strains cause cervical cancer fueled the development of a vaccine to prevent persistent infections with those HPV types. Gardasil, approved by the FDA in 2006, prevents infection with cervical cancer-causing HPV types 16 and 18, as well as genital wart-causing HPV types 6 and 11. A second vaccine, Cervarix, also prevents persistent infections with HPV types 16 and 18. As of June 2011, approximately 35 million doses of Gardasil had been distributed in the U.S. alone[19]. Studies suggest that the vaccines may also reduce the risk of all HPV-related cancers, including those that can occur in the head, neck, and mouth.

Following on this success, researchers began studying whether viruses or other infectious agents might be associated with different cancers and have found additional connections (see **Figure 8**, p. 35). Just as the removal or reduction of the infectious agents that cause cancer should prevent or slow the progression of cancer, vaccinating against cancer-causing viruses is potentially effective and likely to become commonplace.

Continued research in this area holds great promise for our conquest of certain cancers because it is estimated that infectious agents account for approximately 18% of all new cancers worldwide[18].

Infectious Agent	Cancer
Epstein-Barr Virus	Stomach cancers, Hodgkin's and Non-Hodgkin's lymphomas, and nasopharyngeal cancers
Hepatitis B/C virus	Hepatocellular carcinoma
Helicobacter pylori	Stomach cancers
Human Immunodeficiency Virus (HIV)	Kaposi's sarcoma and non-Hodgkin's lymphoma
Human Papillomavirus (HPV)	Cervical, anogenital, head and neck, and oral cancers

Hormones in Cancer

Hormones are associated with modified risk of breast and ovarian cancers. It is now established that postmenopausal hormone replacement therapy, which includes progesterone, increases breast cancer in women who have a uterus, while oral contraceptive use and tubal ligation decrease the risk of ovarian cancer in premenopausal women. Fetal exposure to diethylstilbestrol, a synthetic estrogen, increases the risk of vaginal/clear cell adenocarcinoma in adulthood. The association of hormones with an increase in cancer, particularly of the breast, has led to the approval by the U.S. Food and Drug Administration (FDA) of anti-estrogen therapies to prevent breast cancers in high-risk women (see **Molecularly Based Prevention**, p. 65). However, the role of hormones in cancer causation is even more complex. Plant-based, weak estrogens, such as those derived from soy products, may be beneficial, but only when consumed over a lifetime. Further, new research is probing the influence of hormone-like substances in the environment, like those found in some plastic containers, on cancer causation. This emerging topic illustrates the power of contributing our knowledge of the biology and epidemiology of carcinogenesis to the evaluation of potential harm from modern-day products.

Infectious Agents and Cancer

The discovery that a number of infections, such as human papillomavirus (HPV), hepatitis B and C viruses (HBV and HCV, respectively), potentially cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and *Helicobacter pylori* bacteria, cause a variety of cancers was an advance of major significance in prevention[18]. This new knowledge has informed the identification of high-risk individuals, as well as the development of new methods of prevention and treatment (see **Conquering Cancer by Eliminating Infectious Agents Sidebar**, p. 34 and **Figure 8**, p. 35).

Cancers Due to Five Infections Correspond to 18% of Global Cancer Incidence

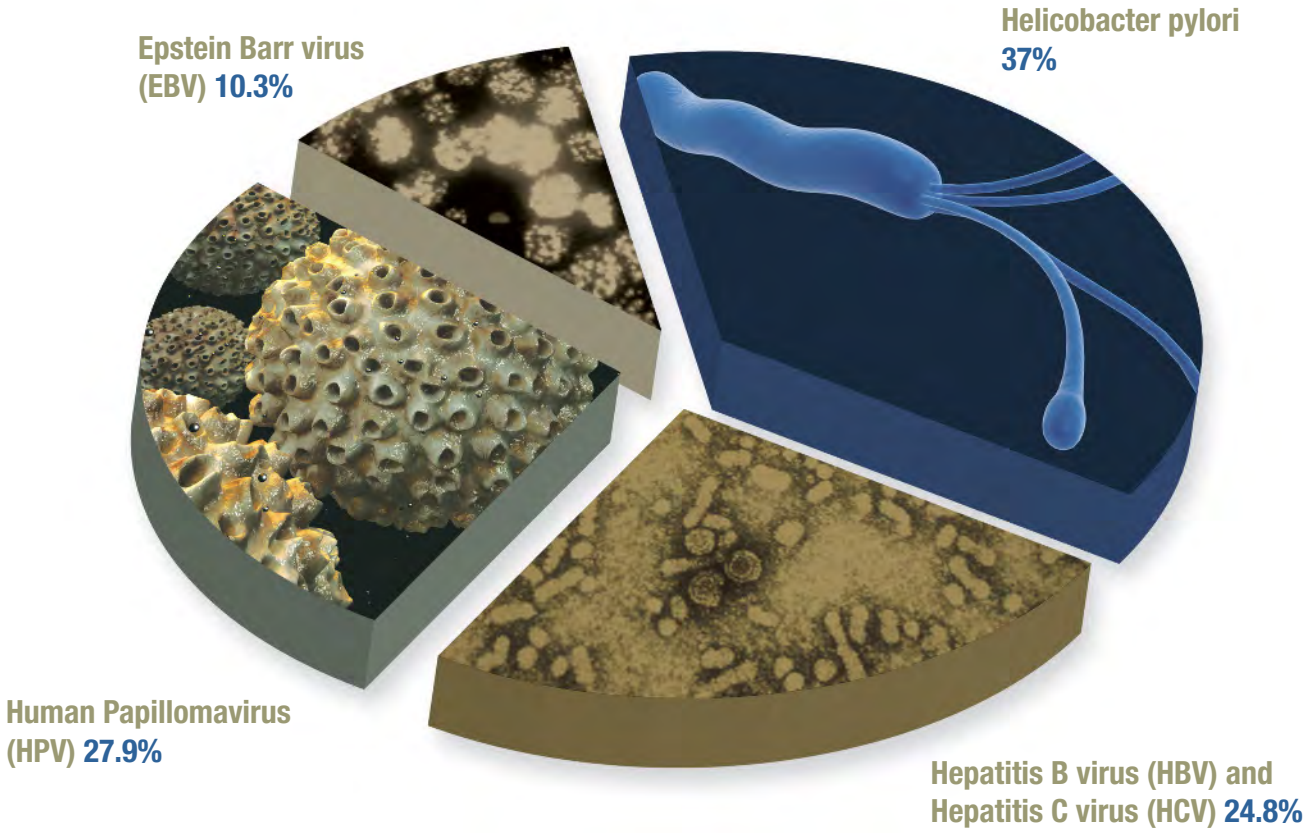


Figure 8: Infectious Causes of Cancer[18]. Globally, more than 18% of all cancer incidences can be attributed to infection with one or more viruses or bacteria, and this is likely an underestimate. Over 80% of stomach cancers are associated with the bacterium *Helicobacter pylori*; at least 80% of liver cancers are associated with Hepatitis B and/or C viruses (HBV or HCV, respectively) infection; at least 25% of cancers of the oral cavity and nearly all cervical cancers are due to human papilloma virus (HPV) family infections; and 10% of stomach cancers, non-Hodgkin's lymphomas, nasopharyngeal cancers, and 30% of Hodgkin's lymphomas are due to Epstein Barr Virus (EBV) infection. These are likely an underestimate, as HPV is also associated with head and neck, as well as anogenital cancers. This total burden does not take into account human immunodeficiency virus (HIV)-associated cancers. It does, however, underscore the fact that immunization or elimination of the underlying infections, when done early, can have a large impact on the global cancer burden.

"The Federal Government, in cooperation with non-Federal organizations, is committed to finding the cause and cure of all forms of cancer and of controlling it to the extent possible while that search goes on."

President Jimmy Carter

Cancer Control Month Proclamation, March 15, 1978

Energy Balance: Weighing in on Cancer

"Energy balance" comprises diet, physical activity, and body weight or body composition, and plays a major role in both cancer risk and recurrence.

A large-scale, long-term epidemiologic study of close to a million men and women confirmed that obesity and being overweight increase overall cancer risk and may account for approximately 90,000 cancer deaths per year in the U.S. That means that about 15% of cancer-related deaths in the U.S. could be prevented if more Americans maintained a healthy weight (Body Mass Index of less than 25 kg/m^2). In addition, regular physical activity, independent of weight reduction, has emerged as a major preventive lifestyle factor, particularly for colon cancer (greater than 30% risk reduction), postmenopausal breast cancer (greater than 30% risk reduction), and endometrial cancer.

Many questions are still unanswered with respect to the role of energy balance in cancer. For example, is it better to be slightly overweight and physically fit, or be thin at any price? What type, frequency, and duration of exercise are most successful in reducing cancer risk? What exercise prescriptions are safe and beneficial for cancer patients? How do we get our Nation's children to increase their physical activity and move around more, especially if they live in unsafe environments? And what biologic mechanisms link energy balance to cancer risk, and how may they provide avenues for clinical or pharmacologic intervention?

In the U.S., the percentage of overweight and obese children has been increasing in recent decades. To respond to the challenge of the obesity epidemic, in 2005 the NIH launched the Transdisciplinary Research on Energetics and Cancer initiative to bring together interdisciplinary research teams to address the topic of energy balance and cancer. Epidemiologists, laboratory scientists, clinicians, psychologists, and scientists from many other disciplines are conducting research to explore the influences of sleep and manufactured environments on energy balance, as well as the activities of fat tissue in producing cancer-promoting factors, the health benefits of exercise versus dieting, and the effects of high-sugar intake (or high-glycemic index diets) on tumor growth.

To date, the cancer research community has responded to this new challenge and shown that regular exercise or weight reduction can reduce biomarkers of cancer risk, including inflammation, estrogen levels, and cellular stress levels, and also normalize insulin levels. Increased insulin signaling has been associated with an increased risk of cancer. As such, several epidemiological studies and clinical trials are evaluating the impact of the anti-diabetic drug, metformin, on a number of obesity-related cancers.

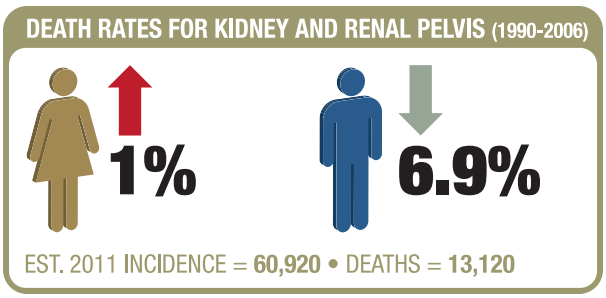
Another major advance has been the discovery that fat tissue itself is metabolically active and secretes hormones that can promote the growth of tumors. In addition, studies suggest that weight loss after cancer detection can improve prognosis and reduce recurrence. For example, a clinical trial showed that adherence to a low-fat diet after initial treatment for early-stage breast cancer reduced the risk of recurrence by about 25% over a 5-year period.

Despite this new knowledge, the obesity epidemic affecting our Nation, and soon the world, clearly remains a major public health challenge and is an area in which continued research efforts are needed.

For example, screening and vaccination for HBV have greatly reduced the incidence of hepatocellular carcinoma in endemic regions. Researchers are actively investigating potential connections between CMV infections and some cases of glioblastoma. Likewise, the treatment and/or elimination of EBV may reduce the minority of stomach cancers not caused by *H. pylori*, Hodgkin's and non-Hodgkin's lymphomas, and nasopharyngeal cancers. The establishment of a link between HPV and cervical cancer in 1974 led to the development and recent FDA approval of two HPV vaccines for the prevention of cervical cancer. Further, an HPV vaccine was recently approved for prevention of anal cancer, and its indications may soon be expanded to head and neck cancers. The effectiveness of the HPV vaccine in preventing cervical cancer is approaching 100%. The extraordinary impact of cancer vaccines has set a high standard for the promise of cancer prevention, and has revolutionized our thinking regarding its potential for saving lives from cancer.

The Role of Diet, Lifestyle, and Other Medical Conditions in Cancer Risk and Recurrence

Numerous studies have shown that diet, physical activity, and body weight or body composition, collectively known as energy balance, play a major role in both cancer risk and recurrence. Medical conditions like obesity and immunosuppression also increase the risk of different cancers (see **Energy Balance Sidebar**, p. 36). Also, excessive intake of alcohol has been shown to increase the



risk of mouth, throat, esophageal, liver, and colon cancers, particularly in men, and of breast cancer in women. Finally, research into the various components of "healthy" foods that may prevent cancer must go deeper and identify the primary component and mechanism of action in order for these compounds to become effective preventive measures (see **Health Behaviors Sidebar**, p. 33).

Together, this means that, conservatively, at least 50% of cancers that occur in the U.S. could be preventable (see **Figure 7**, p. 30). Measurable changes in cancer incidence and mortality can be accomplished by investing in evidence-based behavior modification research and educational campaigns and programs that promote the benefits of a healthy diet, regular exercise, weight loss, smoking cessation, the use of prophylactic vaccines, and the reduction of risky behaviors (see **Behavior Research Sidebar**, p. 32). It is imperative that we continue to build upon our knowledge of the causes of cancer and increase the number of cancers that we can prevent through behavior modification.

Advances in Cancer Detection and Screening

Finding a tumor early, before it has spread to other parts of the body, makes it more likely that cancer can be treated successfully with fewer side effects and a better chance of survival.

Many cancers, particularly those that arise in tissues other than the blood, are progressive in nature. These cancers begin with a series of genetic and cellular changes that cause normal cells to develop into pre-cancerous lesions, called intraepithelial neoplasia (IEN), and end in metastatic disease (see **Figure 9**, pp. 38-39). These processes typically take place over a period of years, and improvements in our ability to identify these changes have allowed us to detect some pre-cancers and intercept them before they become advanced disease. It is believed that continued research into how to intercept the progression from pre-cancer to cancer could make virtually all cancers preventable.

Population-based screening programs, which test generally healthy individuals for potential disease, provide opportunities to intervene in the cancer process as early as possible. Studies have shown that the widespread screening programs implemented in the U.S. have been both beneficial and cost effective.

Screening is routinely done for the early detection of cervical cancer using the Papanicolaou (Pap) tests, for breast cancer with mammography, for prostate cancer using prostate specific antigen (PSA) tests, for colon cancer using colonoscopy, and, most recently, for lung cancer in current and former heavy smokers using spiral computed tomography (CT). To be successful, early detection must lead to reduced cancer mortality.

"Vigorous cancer research, directed to both treatment and prevention, must continue. All of us look to the day when this disease has been eradicated as a major threat to American lives."

President Ronald W. Reagan

Cancer Control Month Proclamation, March 20, 1981

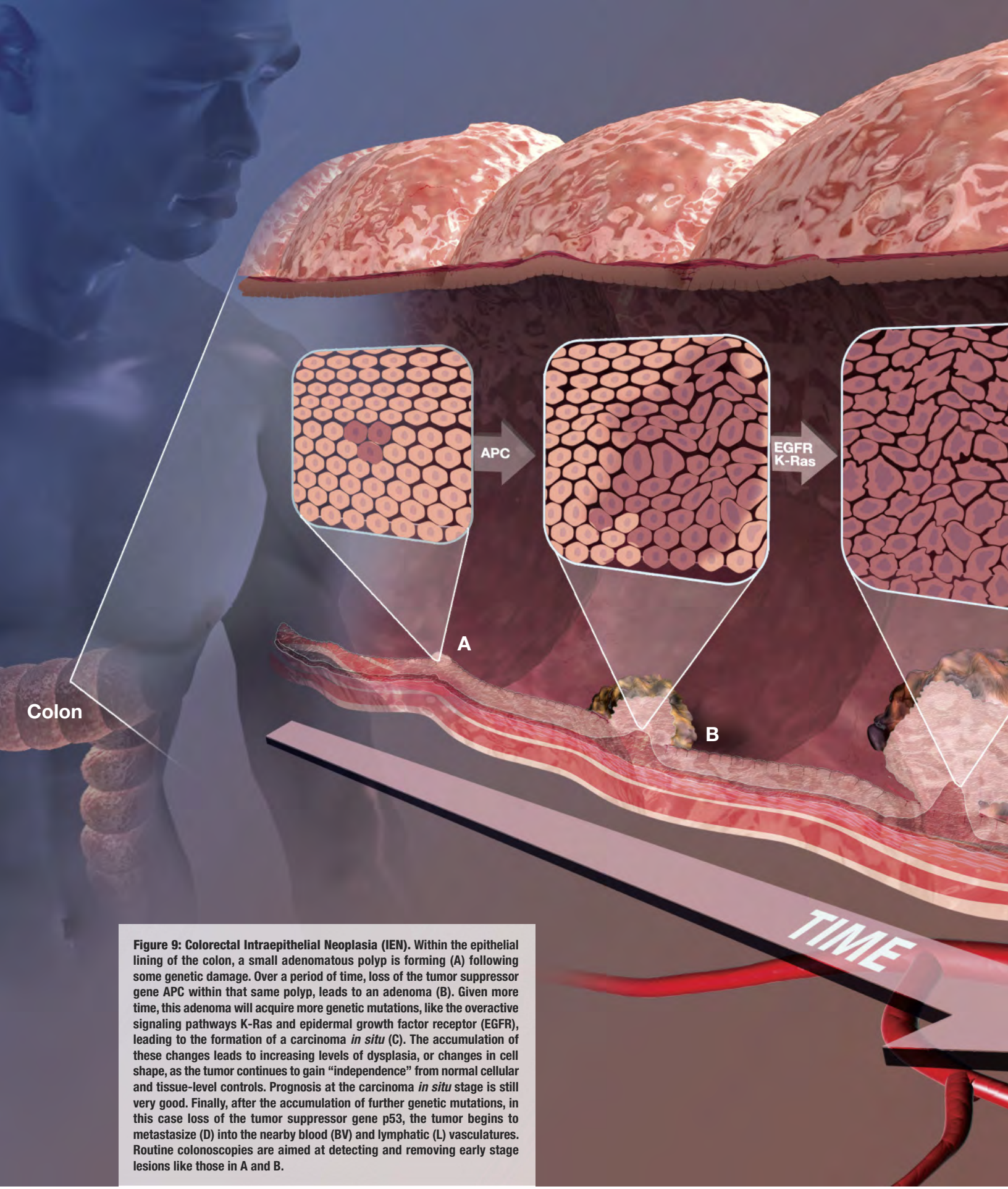
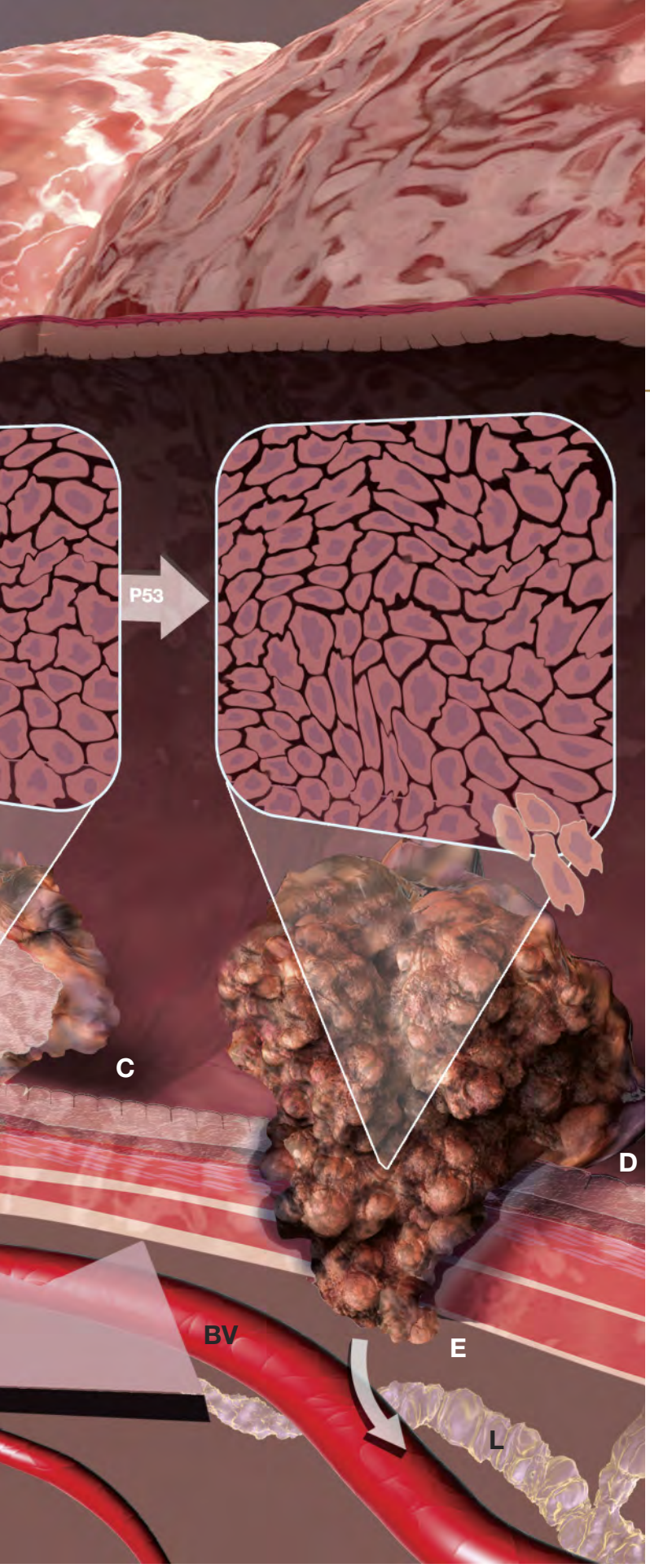


Figure 9: Colorectal Intraepithelial Neoplasia (IEN). Within the epithelial lining of the colon, a small adenomatous polyp is forming (A) following some genetic damage. Over a period of time, loss of the tumor suppressor gene APC within that same polyp, leads to an adenoma (B). Given more time, this adenoma will acquire more genetic mutations, like the overactive signaling pathways K-Ras and epidermal growth factor receptor (EGFR), leading to the formation of a carcinoma *in situ* (C). The accumulation of these changes leads to increasing levels of dysplasia, or changes in cell shape, as the tumor continues to gain "independence" from normal cellular and tissue-level controls. Prognosis at the carcinoma *in situ* stage is still very good. Finally, after the accumulation of further genetic mutations, in this case loss of the tumor suppressor gene p53, the tumor begins to metastasize (D) into the nearby blood (BV) and lymphatic (L) vasculatures. Routine colonoscopies are aimed at detecting and removing early stage lesions like those in A and B.



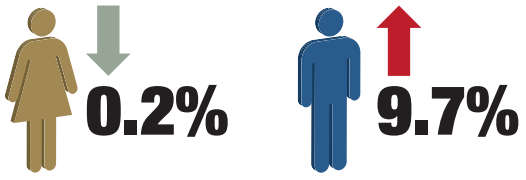
Some tests, such as the Pap test, directly examine cellular shape, or histological analysis, to look for abnormal cells. The Pap test has contributed significantly to the 99% reduction in deaths from cervical cancer in the U.S. by identifying the precancerous cells to allow for their removal, thus preventing the progression to cancer. The PSA screening for prostate cancer has resulted in earlier detection and intervention. This approach leads to fewer severe side effects from treatment and a better quality of life.

Imaging technologies have also improved our ability to detect and screen for cancer. Routine mammography screening, although the results have been variable, has been shown to reduce breast cancer deaths by as much as 29% for women in their 40s. Likewise, colonoscopy detects pre-cancerous polyps so that they can be removed before they develop into advanced disease. This early intervention is estimated to have reduced colorectal cancer deaths by 50%.

Finally, earlier this year, researchers reported that, among current and former heavy smokers, spiral CT screening reduced lung cancer mortality by 20% by identifying small tumors; however, this is an early result and more work needs to be done before it is applied population wide.

New imaging technology will make identifying premalignant lesions and early disease more effective, thus providing opportunities for chemoprevention strategies, more effective

DEATH RATES FOR ESOPHAGEAL CANCER (1990-2006)



EST. 2011 INCIDENCE = **16,980** • DEATHS = **14,710**

Table 2: FDA-Approved Chemicals for the Treatment of Cancer

DNA Synthesis Inhibitors (Anti-metabolites)

Approved Indication	Generic Name	Trade Name
multiple cancers	5-fluorouracil (5FU)	Adrucil
certain leukemias	6-mercaptopurine	Purinethol
breast and colorectal cancers	capecitabine	Xeloda
certain leukemias; lymphoma	cladribine	Litrak; Movectro
certain leukemias	clofarabine	Clolar
certain leukemias; lymphoma	cytarabine	DepoCyt; Cytosar-U
stomach cancer	floxuridine	FUDR
certain leukemias; lymphoma	fludarabine	Fludara
pancreatic cancer	gemcitabine	Gemzar
bladder, lung, and pancreatic cancers	gemcitibine	Gemzar
certain leukemias	hydroxyurea	Droxia
multiple cancers	methotrexate	Rheumatrex; Trexall
multiple cancers	mitomycin	Mutamycin
certain leukemias; lymphoma	nelarabine	Arranon
lung and ovarian cancers; mesothelioma	pemetrexed	Alimta
certain leukemias	pentostatin	Nipent
certain lymphomas	pralatrexate	Folotyn

DNA Damaging Agents

Approved Indication	Generic Name	Trade Name
ovarian cancer	altretamine	Hexalen
certain leukemias	arsenic trioxide	Trisenox
multiple cancers	bendamustine	Treanda
certain lymphomas; squamous cell and testicular cancers	bleomycin sulfate	Blenoxane
certain leukemias	busulfan	Myleran; Busulfex
breast, lung and ovarian cancers	carboplatin	Paraplatin; Paraplat
brain tumors; certain lymphomas	carmustine	BiCNU
multiple cancers	chlorambucil	Leukeran
multiple cancers	cisplatin	Platinol-AQ
multiple cancers	cyclophosphamide	Cytoxan
melanoma; certain brain cancers	dacarbazine	DTIC-Dome
multiple cancers	dactinomycin	Cosmegen
certain leukemias	daunorubicin; daunomycin	Cerubidine
multiple cancers	doxorubicin hydrochloride	Adriamycin PFS; Adriamycin RDF
certain leukemias; breast and stomach cancers	epirubicin hydrochloride	Ellence
prostate cancer	estramustine	Emcyt; Estracyt
certain leukemias	idarubicin	Idamycin PFS
multiple cancers	ifosfamide	Ifex
colon, lung and rectal cancers	irinotecan	Camptosar; Campostar
brain tumors	lomustine	CeeNU
multiple cancers	mechlorethamine hydrochloride	Mustargen
multiple cancers	melphalan	Alkeran
certain lymphomas	methoxsalen	Uvadex
multiple cancers	mitoxantrone	Novantrone
colon cancer	oxaliplatin	Eloxatin
testicular cancer	plicamycin	Mithracin
certain lymphomas	procarbazine	Matulane
pancreatic cancer	streptozocin	Zanosar
melanoma; certain brain cancers	temozolomide	Temodar
certain leukemias	thioguanine	Thioguanine Tabloid
multiple cancers	thiotepa	Thioplex
ovarian and small cell lung cancers	topotecan	Hycamtin
bladder cancer	valrubicin	Valstar

INCREASING PRECISION

Cell Cytoskeleton Modifying Agents

Approved Indication	Generic Name	Trade Name
prostate cancer	cabazitaxel	Jevtana
multiple cancers	docetaxel	Taxotere
breast cancer	eribulin mesylate	Halaven
breast cancer	ixabepilone	Ixempra
multiple cancers	paclitaxel	Abraxane
multiple cancers	vinblastine	Velban
certain leukemias and lymphomas	vincristine	Oncovin
breast and lung cancers	vinorelbine tartrate	Navelbine

Anti-Nutrients

Approved Indication	Generic Name	Trade Name
certain leukemias	asparaginase	Elspar; Kidrolase

Gene Transcription Modifiers

Approved Indication	Generic Name	Trade Name
certain lymphomas	bexarotene	Targretin
certain leukemias	tretinoin (all-trans retinoic acid)	Vesanoid

Hormones/Anti-Hormones

Approved Indication	Generic Name	Trade Name
prostate cancer	abarelix	Plenaxis
prostate cancer	abiraterone acetate	Zytiga
breast cancer	anastrozole	Arimidex
prostate cancer	bicalutamide	Casodex
prostate cancer	degarelix	Firmagon
testicular and lung cancers	etoposide phosphate	Etopophos; Topusar; VePesid
breast cancer	exemestane	Aromasin
prostate cancer	flutamide	Eulexin
metastatic breast cancer	fulvestrant	Faslodex
prostate and breast cancers	goserelin acetate implant	Zoladex
breast cancer	letrozole	Femara
prostate cancer	leuprolide acetate	Eligard; Lupron: Viadur
breast and endometrial cancers	megestrol acetate	Megace; Megace Oral Suspension
pituitary cancer	mitotane**	Lysodren
breast cancer	tamoxifen	Nolvadex
prostate cancer	triptorelin pamoate	Trelstar Depot

Immune System Modifiers

Approved Indication	Generic Name	Trade Name
multiple cancers	interferon alfa-2b	Intron A
melanoma; kidney cancer	aldesleukin	Proleukin
myelodyspalstic syndrome	lenalidomide	Revlimid

Proteosome Inhibitor

Approved Indication	Generic Name	Trade Name
multiple myeloma	bortezomib	Velcade

Epigenetics Modifiers

Approved Indication	Generic Name	Trade Name
myelodysplastic syndrome	azacitidine	Vidaza
myelodysplastic syndrome	decitabine	Dacogen
certain lymphomas	romidepsin	Istodax
certain lymphomas	vorinostat	Zolinza

Angiogenesis Inhibitors

Approved Indication	Generic Name	Trade Name
kidney cancer	pazopanib	Votrient
kidney cancer	sorafenib	Nexavar
gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
thyroid cancer	vandetanib	Caprelsa

Cell Signaling Inhibitors

Approved Indication	Generic Name	Trade Name
lung cancer	crizotinib	Xalkori
some leukemias	dasatinib	Sprycel
some lung cancers	erlotinib	Tarceva
some pancreatic cancers; kidney cancer	everolimus	Afinitor
lung cancer	gefitinib	Iressa
some leukemias; stomach cancer; certain type of skin cancer	imatinib	Gleevec; Glivec
breast cancer	lapatinib	Tykerb
some leukemias	nilotinib	Tasigna
kidney cancer	temsirolimus	Toricel; Torisel
thyroid cancer	vandetanib	Caprelsa
melanoma	vemurafenib	Zelboraf

** mechanism is not completely clear

Some drugs are available in multiple formulations, these have only been listed once.

Where multiple trade names are used, only the most common have been listed.

INCREASING PRECISION

treatments for early disease, and the reduction of cancer mortality. The challenges are to identify the population that will most benefit from these strategies and to determine the optimal frequency of screening. Cost containment so as to make this approach affordable will be essential to its success.

Clearly, screening to detect cancers early can greatly reduce their incidence. Although not all cancers are amenable to screening, cancer research promises to develop molecular biomarkers and other technologies that can serve as indicators of disease and serve as new screening tools to find cancers that currently elude us, like pancreatic and ovarian cancer.

Advances in Cancer Treatment

Over the past four decades we have seen important advances in the primary triad of cancer patient care—chemotherapy, surgery, and radiation—as well as in the provision of supportive or palliative care.

Advances in Chemotherapy

During the past four decades, new types and combinations of cytotoxic chemotherapy drugs, which largely work by stopping rapidly dividing cells, have been widely used in cancer treatment. Despite their side effects, these drugs have led to major increases in the survival of patients with

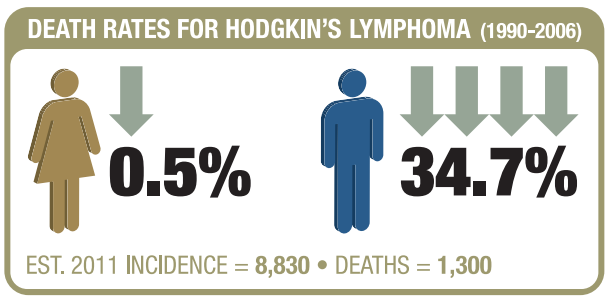


Table 3: FDA-Approved Monoclonal Antibodies for Oncology

Angiogenesis Inhibitor

Approved Indication	Generic Name	Trade Name
colon and lung cancers	bevacizumab	Avastin

Blood Cancer Specific

Approved Indication	Generic Name	Trade Name
certain leukemias	alemtuzumab	Campath
certain lymphomas	brentuximab vedotin	Adcetris
certain lymphomas	ibritumomab	Zevalin
certain leukemias	ofatumumab	Arzerra
certain lymphomas	rituximab	Rituxan
certain lymphomas	tositumomab I131	Bexxar

Cell Signaling Inhibitors

Approved Indication	Generic Name	Trade Name
colon cancer; head and neck cancer	cetuximab	Erbitux
colon cancer	panitumumab	Vectibix
breast cancer	trastuzumab	Herceptin

Diagnostic Antibodies

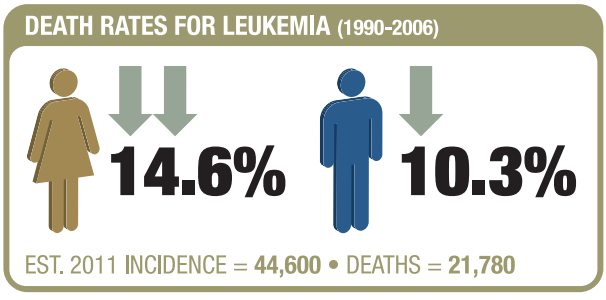
Approved Indication	Generic Name	Trade Name
imaging prostate cancer	Capromab pendetide In111	Prostascint

Immune Stimulator

Approved Indication	Generic Name	Trade Name
melanoma	ipilimumab	Yervoy

Metastasis Inhibitor

Approved Indication	Generic Name	Trade Name
bone metastases	denosumab	Xgeva



childhood acute lymphoblastic leukemia, Hodgkin's disease, aggressive lymphomas, and testicular cancers, to the point of cures or near cures. In addition, significant reductions in death rates have been achieved in breast and cervical cancers in women; prostate and lung cancers in men; and colorectal, oral cavity and pharynx, and stomach cancers in both genders.

Through clinical trials, we have also learned how to use these drugs after surgery or radiation in patients with early-stage disease to significantly reduce the risk of recurrence. These advances have been bolstered by the use of new treatment protocols that combine cytotoxic and other drugs before surgery or radiation, which can shrink the tumor and help ensure that the surgery or radiation maximizes the elimination of tumor cells. Similar principles guide the use of these therapies in the treatment of leukemias and lymphomas, for which surgery has a lesser role. Additionally, anti-hormonal therapies form the basis of treatment for many breast and prostate cancers, and are very successful in reducing the risk of recurrence and mortality (see **Table 2**, pp. 40-41).

Advances in Surgery and Radiotherapy

During the last four decades, surgical procedures have been refined, resulting in fewer disfiguring surgeries with less damage to normal tissue, faster healing times, and better overall recoveries (see **Table 4**, p. 43). This is especially true in breast cancer, where clinical trials have shown that lumpectomy and radiation are as effective as radical mastectomy, and that sentinel node biopsy (which is a way to detect whether the cancer has spread to nearby lymph nodes) is as effective as complete axillary (armpit) node dissection in determining how far a breast tumor has spread and which treatments are needed.

Technological advances have also reshaped surgery. For certain cancers in the abdomen, laparoscopic procedures through which tumors are removed through small incisions

have proved to be as effective as open surgery. In addition, computer-assisted robots perform extremely complex surgeries. For example, computer-assisted advanced prostatectomies further reduce damage to the surrounding delicate nerves and blood vessels, translating into a substantial improvement in quality of life for these patients.

Just as surgery has been improved with the addition of computer guidance, so too has radiotherapy (see **Table 4**, p. 43). Computer-guided machines, like the cyberknife, have markedly improved the precision of radiation therapy, permitting patients to receive increasingly focused and higher doses that can kill more cancer cells with less damage to the surrounding tissue. Also, intensity modulated radiation therapy (IMRT) makes it possible to deliver very high radiation doses to very precise areas, and is now widely used to treat head and neck, and prostate cancers. Similarly, stereotactic radiosurgery, also known as the gamma knife, has made a critical difference in the treatment of various brain and inoperable lung cancers by more precisely treating the tumor and sparing healthy tissue.

Advances in Imaging

As the technologies have improved, so have the imaging capabilities that permit us to diagnose cancer and to determine whether and to what parts of the body a tumor may have spread. For example, positron emission tomography (PET) scans are now used along with a

Table 4: Surgical and Radiotherapy Advances

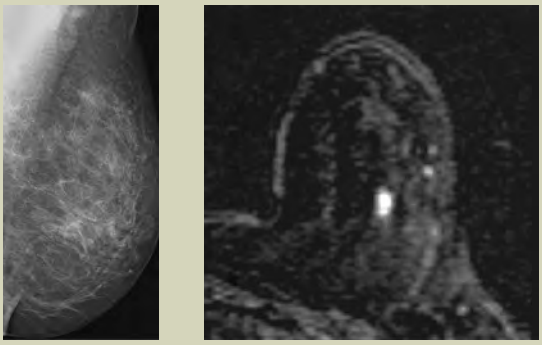
Surgical Advances Used to Treat	Procedure
breast cancer	Mastectomy
breast cancer	Lumpectomy
testicular cancer	Orchiectomy
multiple head, neck and chest cancers	Video-Assisted Thoracoscopic Surgery (VATS)
variety of abdominal cancers	Laparoscopic surgery
sarcoma and other cancers	Reconstructive and limb-sparing surgeries
kidney cancer	Partial nephrectomy
pancreatic cancer	The Whipple/modified Whipple procedure
stomach-sparing pancreatic surgery for pancreatic cancer	Pancreatodudenectomy
rectal cancer	Total mesorectal excision
prostate cancer	Nerve-sparing prostatectomy
rectal cancer	Transanal Endoscopic Microsurgery (TEM)
testicular cancer	Modified retroperitoneal lymph node dissection
breast, melanoma, and colorectal cancers	Sentinel lymph node biopsies
breast cancer, laryngeal cancer, and anal/rectal cancer	Neoadjuvant chemotherapy
multiple cancers	Robotic or computer-assisted surgeries

Radiotherapy Advances Used to Treat	Procedure
prostate, cervical, other cancers	Brachytherapy
multiple cancers	Computer-guided radiation therapy (cyber knife)
brain and some lung cancers	Stereotactic radio surgery (gamma knife)
multiple cancers	Adjuvant/simultaneous radiotherapy
head and neck cancers; prostate cancer	Intensity Modulated Radiation Therapy (IMRT)
rectal cancer	Neoadjuvant radio/chemotherapy
prostate cancer	Adjuvant radiotherapy
pediatric, thoracic, and prostate cancers	Proton Therapy

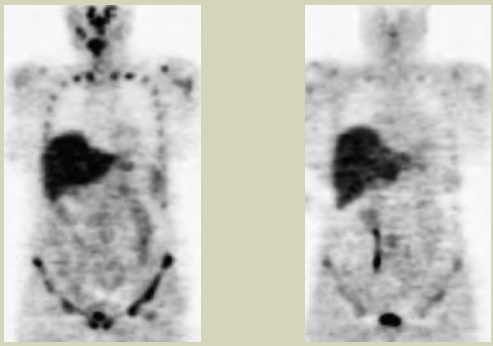
"If you think research is expensive, try disease"

Mary Lasker
Cancer Research Advocate (1901-1994)

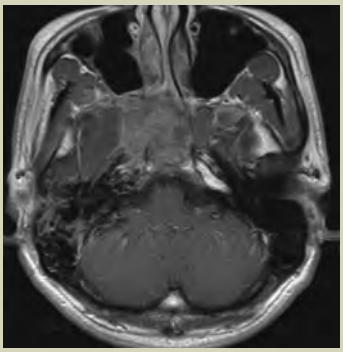
Imaging Modalities for Diagnosis and Imaging Response to Therapy



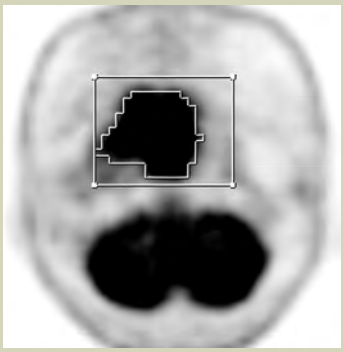
Mammogram MRI A



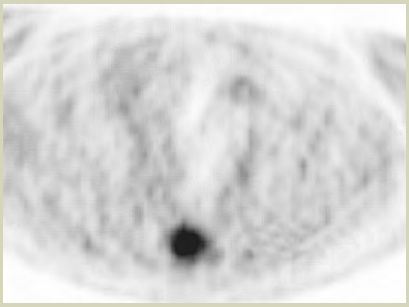
Day 1 Day 4 B



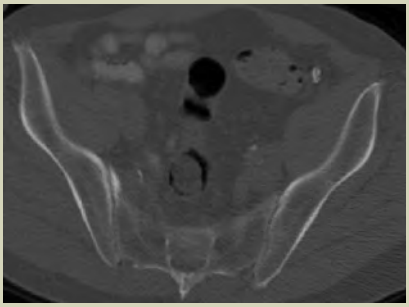
DC-MRI



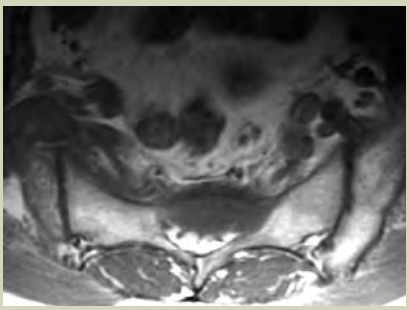
FDG-PET C



FDG-PET



CT



MRI D

Figure 10: Imaging Cancer. Imaging is an increasingly essential part of modern cancer care from routine screening and prevention to informing diagnoses, and more recently to monitor response to therapy both in the clinic and during drug discovery. Not all imaging, however, provides the same quantity or type of information. For example, routine mammography (A, mammogram) detected no cancer, while MRI detected a tumor in the same breast (A, MRI)[20]. Likewise, FDG-PET analysis reveals a bone metastasis (D, FDG-PET), whereas a CT scan detected nothing (D, CT) and MRI analysis is unclear (D, MRI)[21]. New types of imaging like FDG-PET are able to detect metastases (B, day 1) and show the patient's response to therapy (B, day 4)[22]. Increasingly, different types of imaging are being combined to provide the most complete information possible; the use of DC-MRI and FDG-PET (C) reveals the precise location and size of the tumor[23].

radiolabeled glucose tracer, called ^{18}fluorodeoxyglucose (FDG), to identify micrometastases that were previously undetectable by standard imaging techniques, which informs subsequent treatment options (see **Figure 10**, p. 44).

In addition, it is now possible to combine advanced imaging technologies, such as FDG-PET, with CT, or double contrast magnetic resonance imaging (DC-MRI). These combination scans are now being used to simultaneously obtain detailed information about the extent of a patient's cancer and the precise location of metastases, enabling better surgical removal and/or directed radiation of the tumor.

Advances in Supportive Care

A number of palliative or supportive care approaches and technologies have been developed that make the administration of chemotherapy safer and more tolerable.

Anti-emetics have improved the ability of patients to tolerate chemotherapy by reducing nausea and vomiting. The hematopoietic growth factors, which stimulate the production of red and white blood cells in the bone marrow that have been depleted by chemotherapy, have helped prevent severe infections that were common during cancer treatment, allowing for treatment without interruption. Additionally, the class of drugs, known as bisphosphonates, and a new therapeutic antibody, called denosumab (Xgeva; see **Table 3**, p. 42), are now used to reduce bone fractures from metastases of certain cancers to the bone, as well as the metastases themselves.

"Treatments that offer what is seemingly only incremental survival might actually be the ticket to longer-term success, because they may get you to the treatment that ultimately works."

Andrew Messinger
Melanoma Survivor

Finally, our increased understanding of pain management has led to the wider use of analgesics. These drugs have greatly improved the quality of life for patients during and after treatment. This is especially important today as the new therapies and improved management of metastatic disease continue to increase the number of years that patients can survive after initial treatment, thus changing an increasing number of cancers into chronic, manageable conditions rather than a death sentence.

All of these advances have made a real difference in the lives of cancer patients and their families. Because of the molecular revolution, we are now in an era of great promise in our ability to reduce the number of deaths due to cancer and to reduce the suffering caused by this most feared disease.

"This Nation's investment in basic cancer research has led us to an unprecedented understanding of the cancer cell. With this new knowledge, we are undertaking major efforts to prevent cancer; to reverse the process once it starts; to find ways to activate the body's own immune system; and to treat the disease and its symptoms more effectively."

President Ronald W. Reagan

Cancer Control Month Proclamation, April 7, 1986

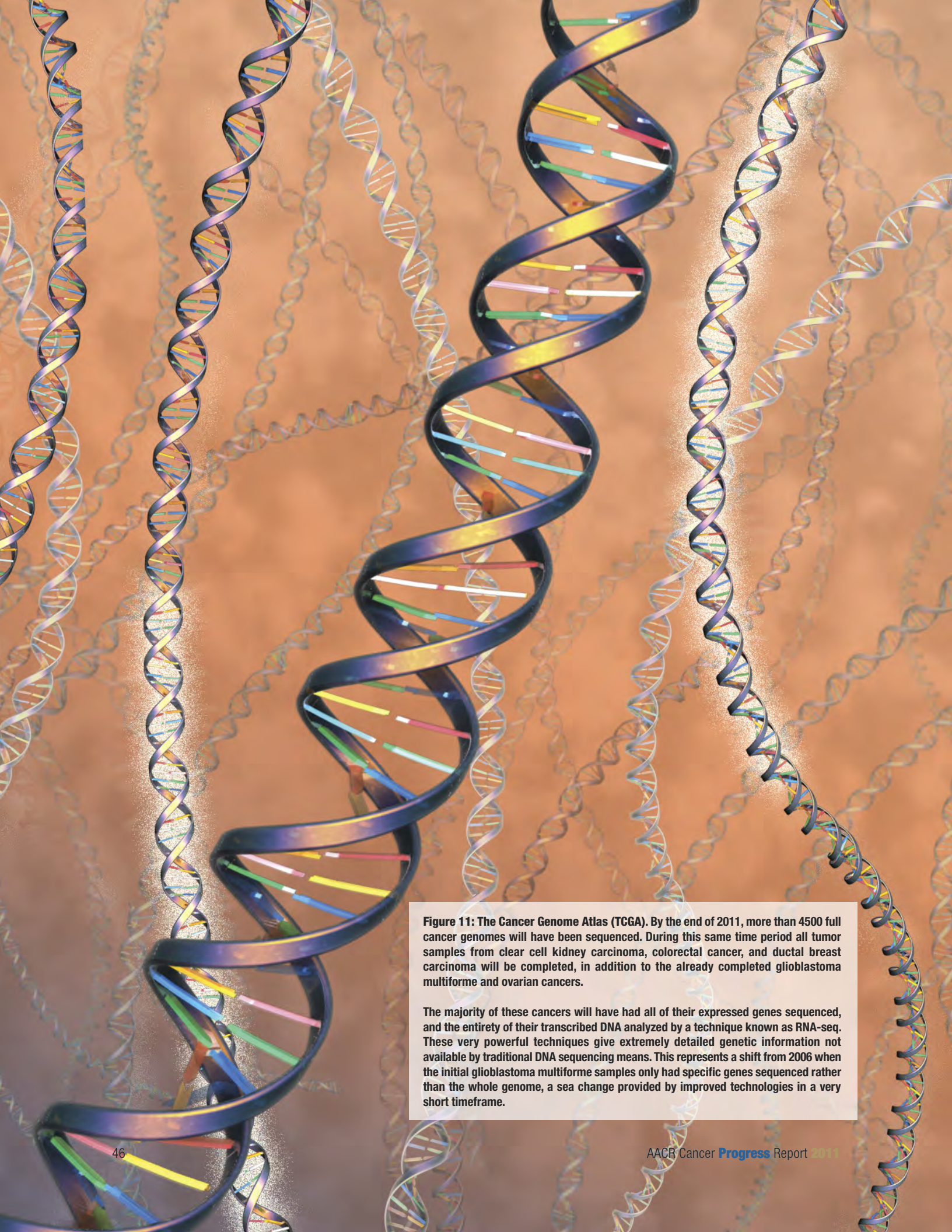


Figure 11: The Cancer Genome Atlas (TCGA). By the end of 2011, more than 4500 full cancer genomes will have been sequenced. During this same time period all tumor samples from clear cell kidney carcinoma, colorectal cancer, and ductal breast carcinoma will be completed, in addition to the already completed glioblastoma multiforme and ovarian cancers.

The majority of these cancers will have had all of their expressed genes sequenced, and the entirety of their transcribed DNA analyzed by a technique known as RNA-seq. These very powerful techniques give extremely detailed genetic information not available by traditional DNA sequencing means. This represents a shift from 2006 when the initial glioblastoma multiforme samples only had specific genes sequenced rather than the whole genome, a sea change provided by improved technologies in a very short timeframe.

Personalized Cancer Medicine:

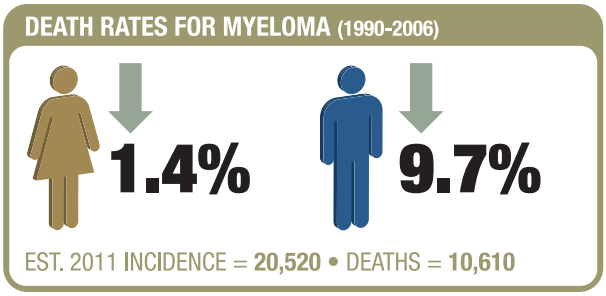
Genomics and Molecular Biology are Transforming Patient Care

The advanced technologies that researchers are using today to sequence cancer genomes, identify altered genes and proteins, and analyze the wealth of information from these technologies are making it increasingly possible to link specific defects in the molecular machinery of cells and tissues to the development of cancer.

As a result, we now have the ability to identify mutations in an individual patient's tumor and use that information to select cancer therapies precisely targeted to these cancer-causing mutations. These discoveries are moving us from an era of one-size-fits-all cancer care to an exciting era of personalized cancer treatment. Knowing the molecular defects in a cancer also promises to identify individuals or populations who may be at increased risk of developing certain types of cancers, thereby reshaping and strengthening our efforts in cancer prevention.

This new era of molecularly based cancer medicine is the culmination of many successes in fundamental or laboratory research and applied research. This progress represents a clear-cut example of the significant return on investment from such research.

We currently stand at a defining moment in our ability to conquer cancer. The molecular biology revolution set the stage for the rapid pace of innovation that has defined the recent decades of cancer research. Exciting fundamental discoveries are occurring at an ever-accelerating rate, and further improvements in cancer patient care and survival will depend in large measure on continued progress in all areas of cancer research.



Molecular Classification of Cancer Subtypes: The Foundation of Personalized Cancer Medicine

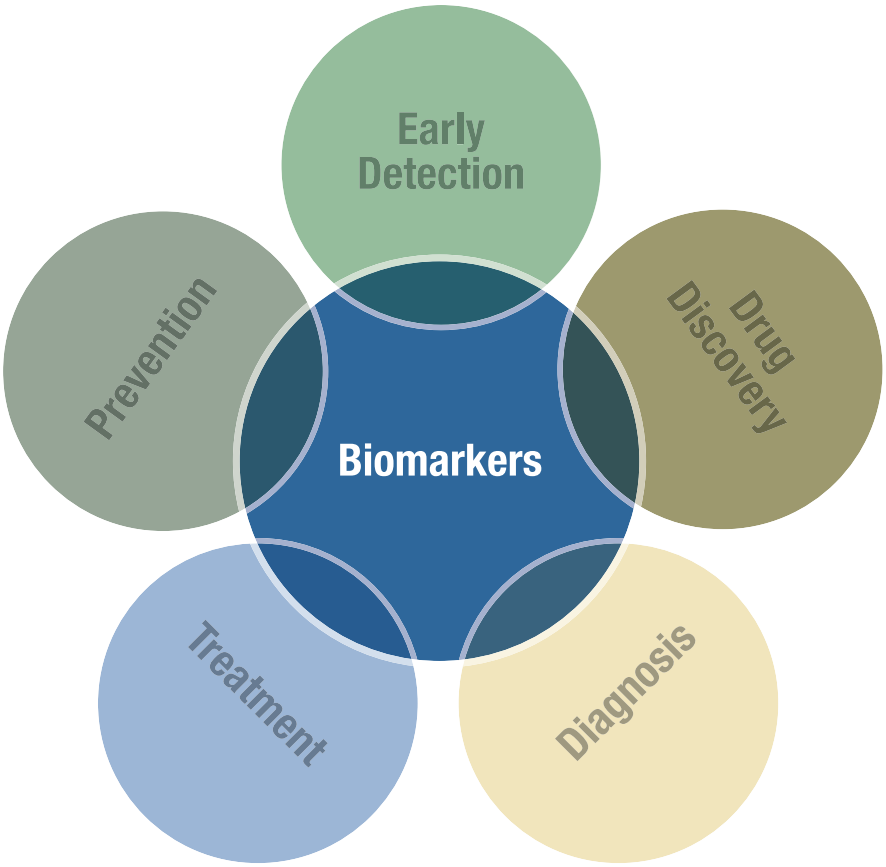
As described above, tumors are now being detected using standard imaging methods, like mammography, MRI, and colonoscopy, as well as more advanced imaging techniques like FDG-PET, DC-MRI, and CT (see **Figure 10**, p. 44). Once detected, a tumor sample that has been obtained by a biopsy is examined by pathologists, who help determine the cancer's stage and grade based on changes in cell shape. We now know that this approach, which has served us for many years, is insufficient when used alone to determine the best course of treatment for most cancers.

Thanks to advanced technologies and progress in genomics and molecular biology, we can now identify the unique molecular characteristics of cancer cells, known as biomarkers. Previously, the organ of origin, such as the lung, brain, etc., defined an individual's cancer. Now, a cancer can be defined by what intrinsic molecular changes drive it. Our ability to identify the genes and molecular pathways that are disrupted in these diseases is providing a new foundation for classifying them into specific molecular subtypes, thus permitting more precise treatment strategies.

To this end, a number of large-scale efforts, such as TCGA, are now underway to identify all of the genomic alterations within specific types of cancer to provide support for the development of biomarkers for these cancers. Early results from TCGA have already revealed previously unknown underlying causes of ovarian cancer and glioblastoma, opening up opportunities for the development of new, much needed treatment strategies for these two cancers that are too often fatal due to the difficulties associated with detecting and treating them (see **Figure 11**, p. 46 and **Vemurafenib Sidebar**, p. 49).

Biomarkers Are the Foundation of Personalized Medicine

Figure 12: Biomarkers Are the Foundation of Personalized Medicine. The molecular characteristics, or biomarkers, of patients and their tumors are the foundation of personalized medicine. Biomarkers are increasingly providing earlier cancer detection, prevention, diagnosis, drug development, and treatment. Continued research into the discovery and use of biomarkers will be essential for continued success in personalized medicine, which will require continued investments in the collection, clinical annotation, storage, and global standardization of biospecimens.



Molecular biomarkers, which may correlate with specific clinical aspects of the tumor, are ushering in a new paradigm for designing and developing more effective and less harmful drugs, known as targeted drugs or therapeutics. Further, these biomarkers are having an impact on all aspects of cancer care including prevention, early detection, diagnosis, treatment, and drug development (see **Figure 12**, p. 48). As a result, we are now beginning to understand why two patients with a disease like lung cancer may have two very different diseases at the molecular level, requiring two entirely different courses of treatment. The development of targeted cancer therapies based on an individual's molecular subtype is progressing quickly and, in doing so, is driving the development of a new generation of clinical trials and providing new hope for cancer patients at high risk for recurrence following standard therapies.

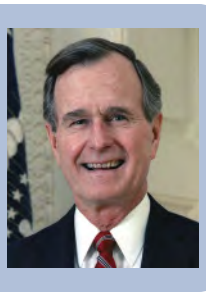
Molecularly Based Drug Design

The development of life-saving or life-improving cancer drugs is essential to our ability to control cancer (see **Figure 13**, p. 50). Traditionally, cancer drugs were made by

"Two decades of intensified research have borne fruit in every aspect of our national effort to reduce the toll cancer takes on our society."

President George H. W. Bush

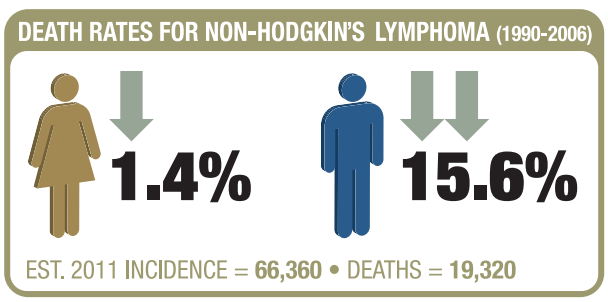
Cancer Control Month Proclamation, April 12, 1991



chemists and then tested in models where they were evaluated for their ability to stop cancer cell growth. If these tests were passed, the compounds entered clinical trials. Because these traditional chemotherapy drugs were developed to stop both rapidly dividing healthy and cancer cells, unfortunately, due to toxicity, they have debilitating short- and long-term side effects.

Our increased understanding of cancer biology, which has been made possible by advances in genomics and molecular biology, has forever changed the way cancer drugs are developed and tested, and it has created research opportunities to develop more effective drugs that have the potential to increase survival in many cancers that previously eluded treatment. These drugs are available to patients because of the investment of hundreds of millions of dollars by the pharmaceutical and biotechnology industries.

Presently, once a molecular alteration fueling a cancer's growth is identified, drugs to target this precise alteration can be developed. This method of drug development, called rational drug development, differs significantly from the development of traditional chemotherapies in that the compounds are designed using computers to most closely match their intended targets. Rationally developed drugs approach a level of precision that has never before been seen in medicine (see **Table 2**, pp. 40-41). Because of this precision, rationally designed cancer drugs that target cancer cells specifically lessen and, in many cases,



Vemurafenib (Zelboraf): Translating Genetic Discoveries into Effective Patient Treatments

Each year, about 68,000 people in the U.S. are diagnosed with melanoma, the most aggressive form of skin cancer[1]. The majority of these cases are diagnosed at an early stage, before the cancer has spread to other parts of the body. In these instances, the tumor is generally surgically removed, leaving the patient cancer-free. The story is very different, however, for patients with melanoma that has metastasized.

With a 5-year survival rate of only 15%, metastatic melanoma is largely responsible for about 8,000 melanoma deaths annually (see **Table 1**, p. 13). The standard treatment for melanoma has involved two drugs that are only effective in just 10 to 20% of patients and do not improve overall survival.

Today, new hope has surfaced in the form of an exciting new drug, called vemurafenib (Zelboraf), which targets a genetic mutation present in about 50% of melanoma patients (see **Table 2**, pp. 40-41)[24].

The story of this drug can be traced back to the 1980s, when researchers first identified the *RAF* gene as an important component of a signaling network that caused virally induced cancers in mice. This discovery led researchers to look for similar mutations in the human version of *RAF* in various cancers.

It was not learned until 2002, when aided by new genetic screening technologies, that about 50% of patients with melanoma carry a mutation within a specific *RAF* gene, called *BRAF*. Of these patients, nearly 90% have a particular mutation known as B-Raf V600E, which causes the B-Raf protein to continually activate its signaling network leading to cancer[24].

Armed with this new knowledge, researchers developed vemurafenib, which works by specifically inhibiting the overactive B-Raf V600E, thereby blocking its ability to cause cancer. When compared with the current standard of care, clinical trials using vemurafenib have confirmed that this drug reduces disease progression by 74% and reduces the risk of death by 63% in patients with inoperable, advanced melanoma during the period investigated[25]. Vemurafenib received FDA approval for the treatment of late-stage melanoma in August 2011.

Importantly, this finding may also soon offer hope for patients with other types of cancer. The same genetic mutation that vemurafenib targets in melanoma patients is also present in 40% of papillary thyroid tumors, 30% of serous ovarian tumors, and 10% of colorectal and prostate tumors.

Vemurafenib is the first example of a drug that has arisen from systematically looking for mutations associated with a particular cancer. All in all, it took only a decade to turn the basic discovery of the melanoma mutations into an FDA-approved therapy for advanced melanoma patients as compared with the discovery of imatinib which took 4 decades from the time of the basic science discovery to FDA approval. This is a remarkable achievement that showcases how knowledge gained over the last couple of decades of fundamental and clinical research, combined with the introduction of new technologies, is now culminating in life-saving therapies. This is a window into the bright future of personalized cancer medicine.

Drug Discovery and Development Timeline

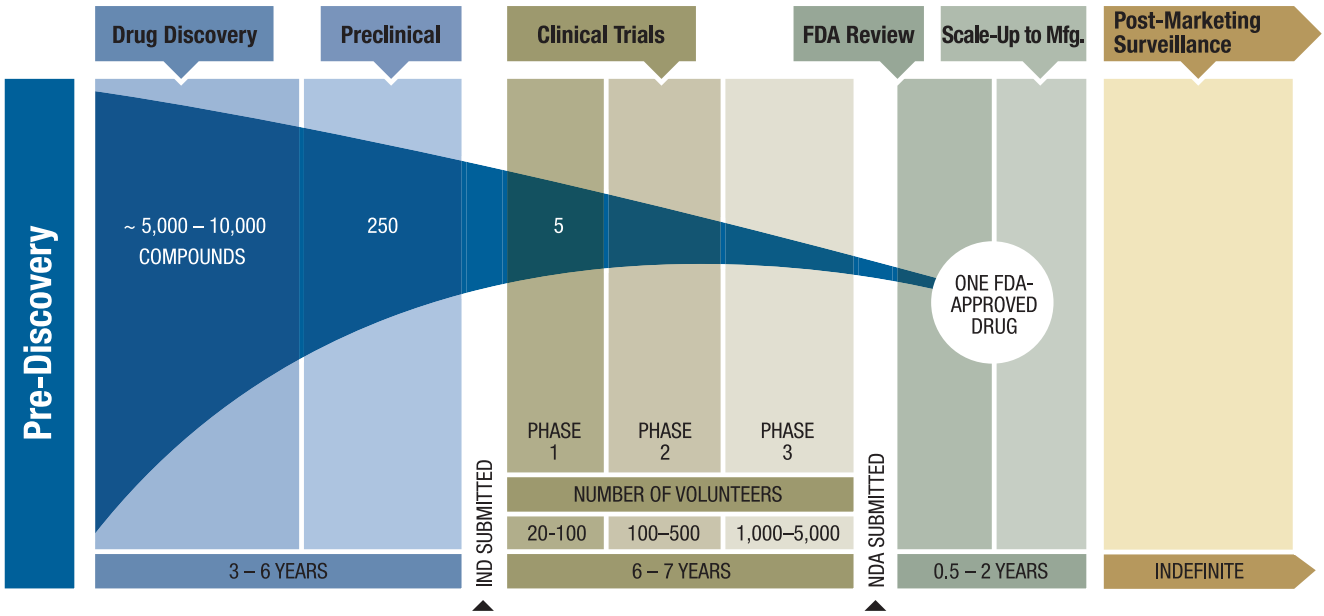


Figure 13: Drug Development: A Long, Difficult, and Complex Process. Drug targets and ideas for targets are identified in laboratory research in both public and private laboratories during the pre-discovery phase of drug development (blue pre-discovery rectangle). In the early drug discovery phase, chemical or biological agents are screened to identify the subset of molecules that effectively hit their targets (blue drug discovery rectangle); there may be between 5 and 10,000 compounds during this stage yielding 250 that proceed to the next (blue preclinical rectangle). At this stage, these compounds are subsequently screened for activity in disease-specific laboratory and animal models, which may yield only as few as 5 compounds that can be taken into the clinic (olive clinical trial rectangle). At this stage, the company or companies bringing these molecules forward must get permission to test them in humans. This is done via an investigational new drug application (IND) with the FDA; a successful IND allows the compound(s) to be tested in patients on clinical trials (olive Phase 1, 2, and 3 rectangles). Clinical trials are multi-year assessments of the safety and efficacy of drugs, requiring increasing amounts of patients as the trials proceed; see Molecularly Based Clinical Trials, and Figure 18. If a compound is successful for a given disease (indication), then the company can file for a new drug application (NDA), at which time the FDA will review the application and either approve or reject the drug based on the results of the clinical trials; in some cases, the FDA will require further testing before approval can be granted (green FDA review rectangles). If the drug is granted approval, a market authorization is given, and the company can begin marketing and selling the drug (green FDA review rectangles), once they have produced enough of the drug to meet patient demand (green scale-up rectangle). Once a drug is on the market, physicians and patients are encouraged to report any adverse reactions so that they can be followed by the FDA and further investigation performed, if necessary; this is the post-marketing surveillance period, also known as pharmacovigilance (gold post-marketing surveillance rectangle). Adapted from www.phrma.org.

eliminate drug toxicity. Today's advances in drug development, clinical trial design, and treatment are the result of our ability to identify the biomarkers associated with the molecular subtypes of cancer and rationally design drugs to precisely target them.

However, to fully realize the advantages of biomarkers in research and care, the fundamental problems inherent in turning discoveries into drugs that benefit patients must be addressed. Typically, drug development is complex, high-risk, and time-consuming, and all too often new promising agents never make it through to full development into the clinic, becoming lost in a gap that some refer to as the "valley of death." This gap arises when promising discoveries lack sufficient investment to develop them into new FDA-approved therapeutics or diagnostics. Steps must be taken to address this challenge.

One potentially effective way to bridge this gap would be to increase pre-competitive collaboration among all sectors in the field - academia, government, the biotechnology and pharmaceutical industry, philanthropic organizations, and patient advocacy groups - that are involved in the drug development process. Other potentially synergistic, worthy

ideas almost certainly exist and need to be vetted in order to effect real change in this complex problem.

The research that underpinned advances in genomics and powered the molecular biology revolution has demonstrated what is possible when a country agrees to invest in science, technology, and innovation. However, this visionary strategy also underscores the need to develop the infrastructure necessary to support molecularly based medicine: a robust network of high-quality, clinically annotated tissue samples, or biospecimens, collected using global standards in privacy protection and archiving; and platforms in genomics and proteomics with the accompanying informatics for data analysis and communication between research laboratories. The effectiveness of both molecular classification of tumors and targeted drug development, for the benefit of patients everywhere depends on the availability of biospecimens that are properly consented, collected and annotated.

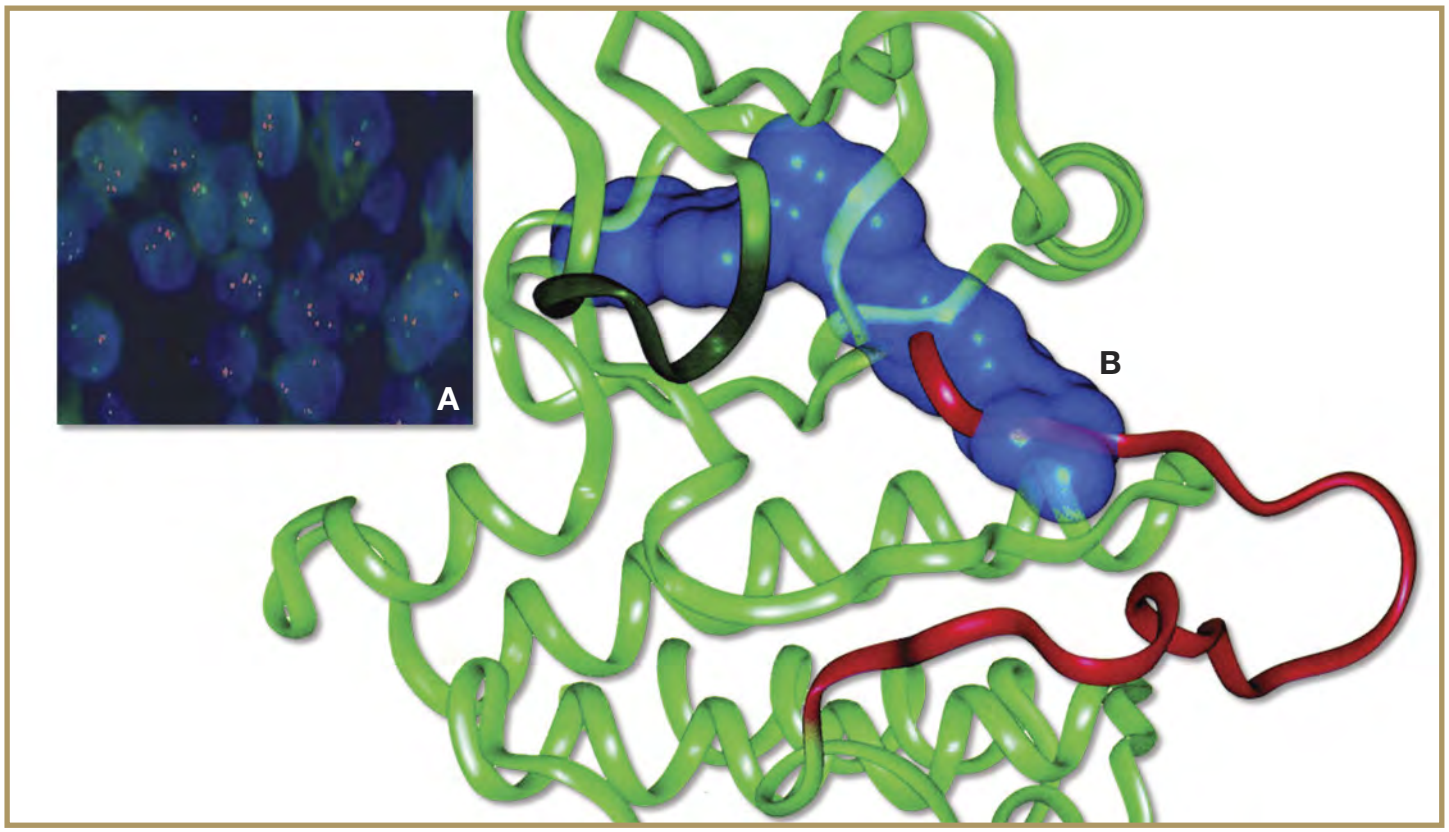


Figure 14: Development of Imatinib (Gleevec). Improvements in microscopy and chromosomal characterization led to the groundbreaking discovery that patients with CML had a specific chromosomal rearrangement, now known as the Philadelphia chromosome (pink dots, A)[26]. This rearrangement produces a fusion of two chromosomes that creates a novel protein kinase, called BCR-Abl (green ribbon, B) that is responsible for the immune cells' uncontrolled growth. Technologies for chemical-based screens, structural biology, and libraries of inhibitor compounds made it possible for public and private research collaborations to design and test chemicals (blue structure, B) that could block the activation of BCR-Abl (red ribbon, B)[27]. Thus, imatinib (blue structure, B) became the first rationally designed oncology drug; see **Imatinib Sidebar**, p. 52.

Imatinib (Gleevec): The Dawn of a New Era in Drug Development and Cancer Care

Chronic myelogenous leukemia (CML) is a bone marrow cancer that results in an accumulation of white blood cells in the blood. A diagnosis of CML was akin to a death sentence until 2001, when a novel drug, called imatinib mesylate (Gleevec), was approved by the FDA. Now, the 5-year survival rate for CML has climbed to 95%[1].

The discovery of imatinib is significant because it was the first FDA-approved rationally designed oncology drug and it founded an entirely new therapeutic class of drugs, called kinase inhibitors. Further, it became the proof-of-concept for targeted therapeutic drugs. The scientific discoveries that led the development of imatinib illustrate how our ability to identify a tumor's underlying biology makes it possible to create a targeted cancer therapy.

The story of imatinib began in 1960, when researchers reported that cells taken from patients with CML had a specific chromosomal rearrangement, now known as the Philadelphia chromosome (see **Figure 14**, p. 51). Improvements in microscopy and chromosomal characterization led to the groundbreaking discovery in 1973 that these rearrangements produced a fusion of two chromosomes. This fusion was later found to create a novel fusion protein, called BCR-Abl, a kinase, which alters the signaling network controlling a cell's growth. Researchers showed that BCR-Abl functioned as an oncogene and caused leukemia when expressed in mice. These discoveries led researchers to theorize that inhibiting the activity of BCR-Abl could prevent the uncontrolled cell growth seen in CML patients.

In the 1990s, technologies for chemical-based screens, structural biology, and libraries of inhibitor compounds made it possible for public and private research collaborations to design and test chemicals that could block BCR-Abl (see **Figure 14**, p. 51). The result was imatinib, which was first tested in humans in a small Phase I study in 1998. Even in these early studies, it was clear that the effects of imatinib were profound. Due to its ability to inhibit BCR-Abl, imatinib was approved by the FDA for the treatment of CML in 2001, and is now also approved for all phases of adult CML, pediatric CML, acute lymphoblastic leukemia, and chronic eosinophilic leukemia/hypereosinophilic syndrome.

Researchers were delighted when upon further study it was found that imatinib also inhibits the related kinases, KIT and PDGFR. Based on this understanding, imatinib was tested in patients with cancers with mutant forms of KIT or PDGFR. As a result, imatinib is now also approved for the treatment of gastrointestinal stromal tumors, aggressive systemic mastocytosis, dermatofibrosarcoma protuberans, and myelodysplastic syndrome/myeloproliferative disease.

The continued development of rationally designed cancer drugs will ensure that, in the future, patients with many other types of cancers will benefit from these life-saving compounds.

The Dawn of Molecularly Driven Drug Design

A powerful example of the dramatic changes in drug development that we are now witnessing began not long after the signing of the National Cancer Act, when researchers discovered that a molecular defect due to a chromosomal translocation in a majority of patients with chronic myelogenous leukemia (CML) correlated with the production of a novel signaling enzyme, called a kinase, that caused the overproduction of certain blood cells. This discovery propelled researchers across disciplines to collaborate on the development of both a detailed computational analysis of protein structures and a large collection of new agents that could block these abnormal kinases. Through this process, the first rationally designed oncology drug, imatinib (Gleevec), was developed (see **Gleevec Sidebar, Table 2**, and **Figure 14**, pp. 52, 40-40, 51, respectively).

Imatinib proved that drugs could be purposefully developed to block the activity of a specific kinase target, and its success was the catalyst for the 13 FDA-approved kinase inhibitors now being used to treat a variety of cancers, as well as other drugs now in development or in clinical trials (see **Table 2**, pp. 40-41). Kinase inhibitors are part of a much larger family of drugs, called small molecule inhibitors, many of which are being developed using a similar rational design approach. The development of Imatinib for the treatment of CML revolutionized drug development, spawning several classes of new drugs that are now being used in the clinic to treat cancer and other diseases (see **Table 2**, pp. 40-41).

The Use of Biological Agents to Treat Cancer

Some of the cancer biomarkers that researchers have discovered are proteins, called growth factor receptors. These receptors sit on the surface of cells, where they interact with proteins on the outside of the cell and relay signals into the cell. Within the cell, each signal is relayed

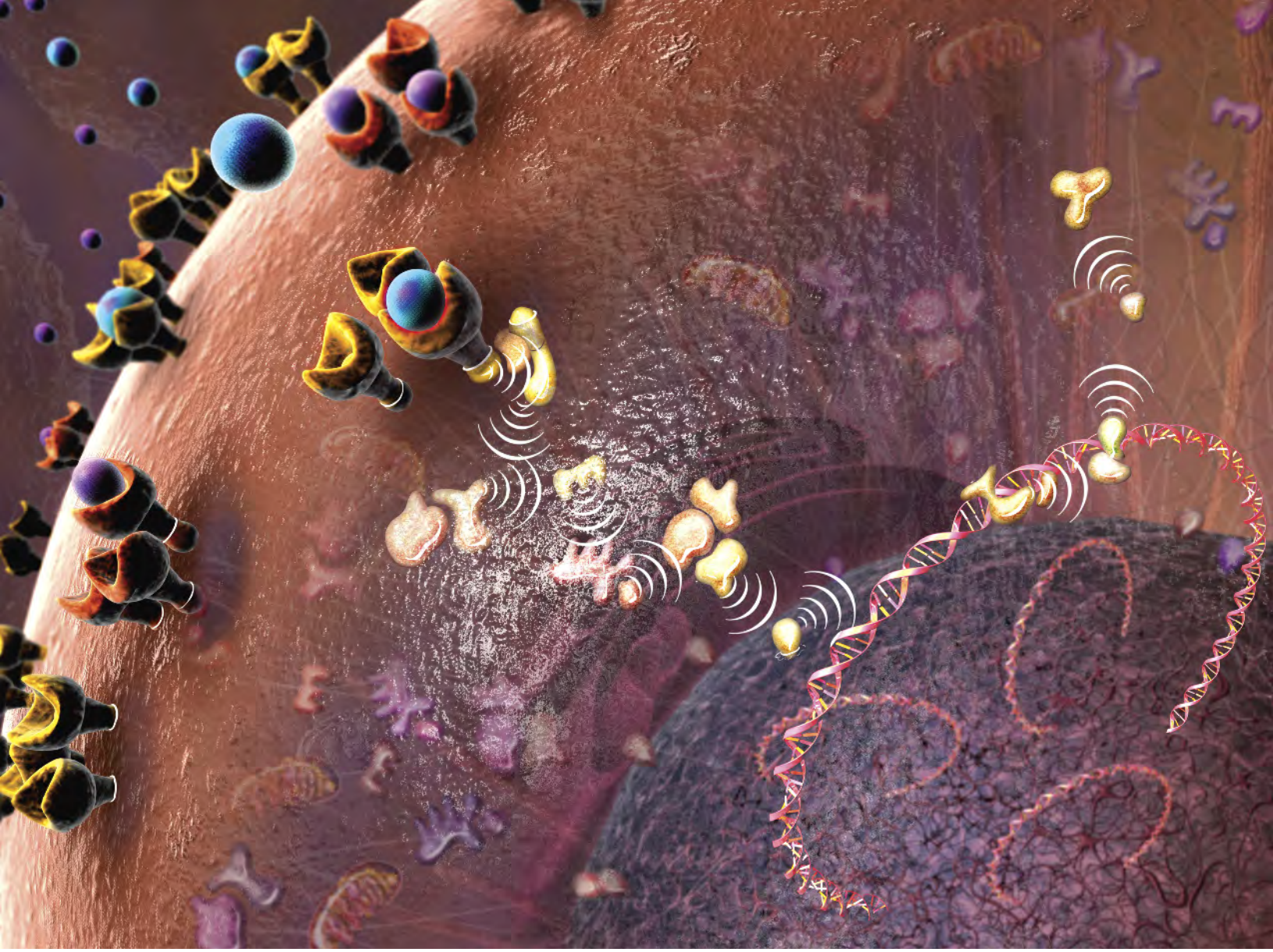
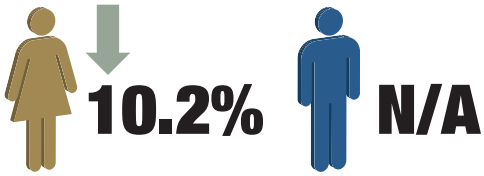


Figure 15: Receptor Tyrosine Kinase Cell Signaling. One way in which cells communicate is through growth factors. These growth factors (blue and purple spheres) bind to specific receiving proteins, called *receptors* (orange and yellow cup-like structures). These receptors sit on the surface of cells and, working in clusters, relay the growth factor signal into the cell. Within the cell, the signal is further relayed across an extensive network of proteins by kinases (lightly-colored blob shapes), eventually changing the activity of genes (DNA) in the nucleus (N) and thus, ultimately, cell behavior. Many identified oncogenes are kinases within these networks, and both they and their receptors are very effective drug targets; see **Tables 2 and 3, pp. 40-41 and 42.**

across an extensive network by kinases, ultimately resulting in changes in the cell's behavior (see **Figure 15**, p. 53).

Antibodies are also proteins that are naturally made by a type of immune cell, called a B-cell. Their role in normal cells is to identify and kill foreign invaders, such as viruses and bacteria. Researchers undertook a strategy to block the activity of the specific receptors driving certain cancers by developing therapeutic antibodies that block receptor function and thereby halt tumor growth (see **Figure 16**, pp. 54-55). The increased function of these receptors and their signaling networks are the result of genetic changes specific to the cancers in which they occur. Therapeutic antibodies can be used alone, or in combination with chemotherapy, to treat different types of cancers. Researchers have also devised ways to attach chemotherapy drugs or radiation-emitting particles to therapeutic antibodies in order to deliver them directly to the cancer cells and avoid damaging normal cells.

DEATH RATES FOR OVARIAN CANCER (1990-2006)



EST. 2011 INCIDENCE = **21,990** • DEATHS = **15,460**

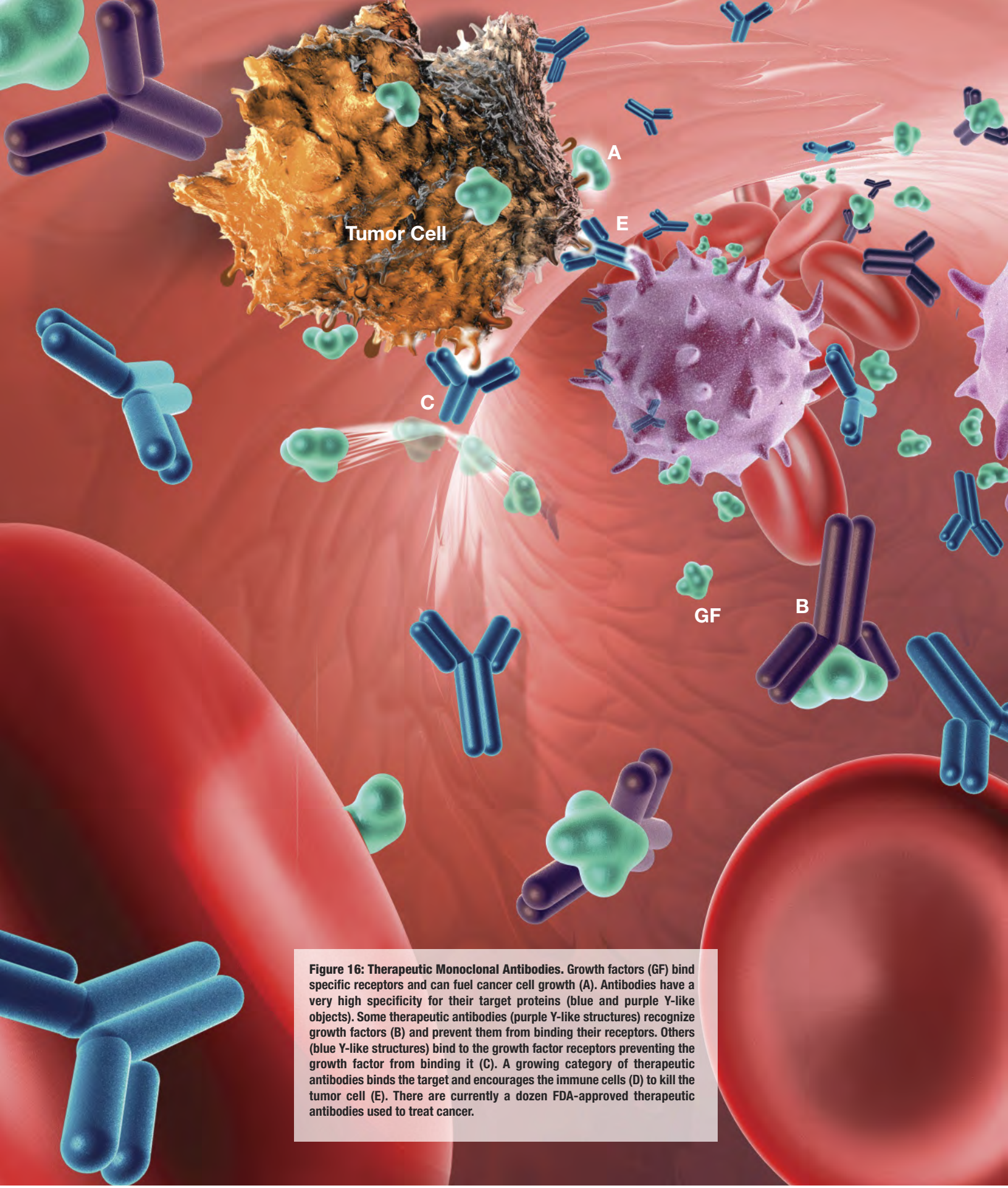
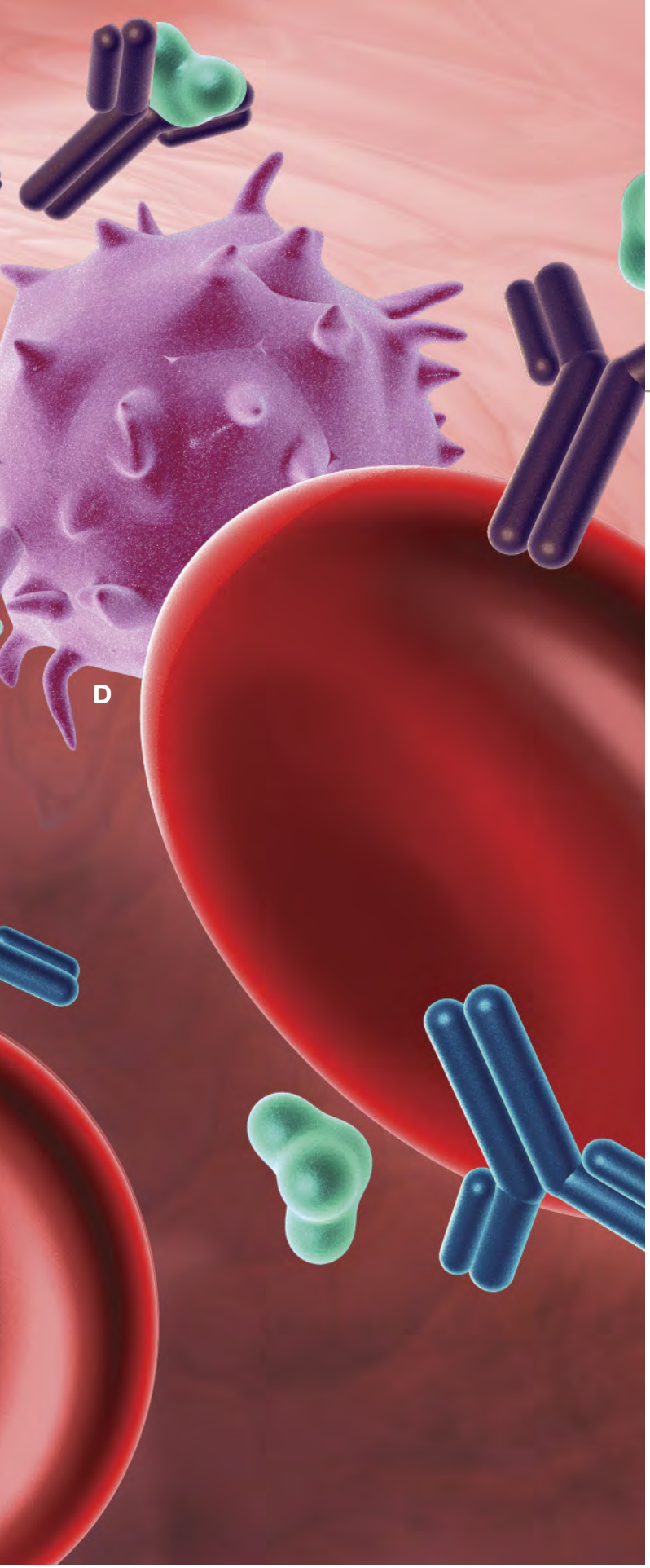


Figure 16: Therapeutic Monoclonal Antibodies. Growth factors (GF) bind specific receptors and can fuel cancer cell growth (A). Antibodies have a very high specificity for their target proteins (blue and purple Y-like objects). Some therapeutic antibodies (purple Y-like structures) recognize growth factors (B) and prevent them from binding their receptors. Others (blue Y-like structures) bind to the growth factor receptors preventing the growth factor from binding it (C). A growing category of therapeutic antibodies binds the target and encourages the immune cells (D) to kill the tumor cell (E). There are currently a dozen FDA-approved therapeutic antibodies used to treat cancer.



The innovative technologies that researchers use to produce large quantities of human antibodies in mammalian cells have made it possible for researchers to develop an entirely new class of drugs, called therapeutic antibodies. Now more than a dozen therapeutic antibodies have been approved by the FDA for use against a number of cancers, and many more are in clinical trials (see **Table 3**, p. 42). Moreover, researchers have discovered that some of the antibodies used for oncology could be used to treat other diseases, like rheumatoid arthritis, providing an enhanced and unexpected return on investments in cancer research.

Molecularly Based Treatment Advances

Our enriched understanding of cancer biology is providing insights into the differences between normal cells and cancer cells. A detailed understanding of the intricate network of signals that control how a cancer cell functions, combined with advances in drug development, now makes it possible to precisely target these differences in order to treat only the cancer cells while minimizing damage to healthy cells. Using molecular tests, we can increasingly match patients to targeted drugs with pinpoint accuracy, and we are at the initial stages of learning how to predict which of these patients will respond best to which drugs. All of these advances have already made a real difference in the lives of a growing number of cancer patients, the 12 million cancer survivors in the U.S., and their families and loved ones.

DEATH RATES FOR ORAL CAVITY AND PHARYNX (1990-2006)

EST. 2011 INCIDENCE = **39,400** • DEATHS = **7,900**

Bonnie Olson

Age 62
Estero, Fla.

"We've found that you have a lump and it *must* come out." These were the words that I heard, dazed and terrified, in 2003. The radiologist didn't ask if I had a ride home or if there was anyone with me in the waiting room. When I shared the news with my husband, we were panic-stricken. Our only previous experience with breast cancer was the death of my sister-in-law. It wasn't until I met with a surgeon the following week that I was told, "This doesn't have to be a death sentence."

My treatment began with a lumpectomy, but when my surgeon determined that some cancer cells remained and that the sentinel node was cancerous, I chose to undergo a double mastectomy and chemotherapy. Later, I learned that because I was HER2-positive, I was eligible to participate in a clinical trial for trastuzumab (Herceptin), which at the time was approved to treat only patients with metastatic disease (see **Molecularly Based Treatment Advances**, p. 56). I wanted to do everything I could to help protect my daughter from going through what I had gone through, and I decided to participate. During the trial I experienced side effects, such as aching bones and tingling feet, which went away a year after my treatment ended. Going forward, I will be monitored for 10 years to find out if my therapy has caused any adverse effects on my heart; so far, I have had none.

As it turned out, the trastuzumab trial I joined became one of the definitive studies that established the drug as a game-changing agent in the fight against HER2-positive breast cancer. A 4-year follow-up study showed that trastuzumab significantly reduces the risk of cancer recurrence and has improved survival by about 24%[28]. It is now a standard part of therapy regimens for patients with HER2-driven tumors.

Today, I am an 8-year breast cancer survivor dedicated to helping other women combat the disease through my involvement at the Susan G. Komen for the Cure Southwest Florida Affiliate. My story is exciting to share with those affected by breast cancer because I recovered. Unfortunately, this is not the case for all women with HER2-positive breast cancer. Important research advances have been made, but funding is more crucial than ever because important challenges remain. Some HER2-positive breast cancer patients are unresponsive to trastuzumab or develop resistance to it; treatment toxicities threaten other survivors.

When we consider that HER2-positive tumors represent only about 20% of all breast cancers—and remaining questions surround all breast cancer subtypes—it is even more apparent that significant, ongoing federal investment in breast cancer research is crucial. We must continue to make advances and not lose momentum when breast cancer is the most frequently diagnosed cancer in women.

Epigenetic Targets

Epigenetics is the study of how the DNA is modified and packaged into chromosomes within a cell. The discovery that epigenetic changes can drive cancer (see **Figure 1**, pp. 20-21) has resulted in 4 new FDA-approved drugs that target epigenetic processes for the treatment of certain leukemias, cutaneous T-cell lymphoma, and myelodysplastic syndrome, the latter of which occurs when cancer of the stem cells within the bone marrow fail to produce adequate numbers of normal blood cells (see **Table 2**, pp. 40-41). For the treatment of myelodysplastic syndrome, these epigenetic drugs are now the standard of care. Moreover, several Phase I and II clinical trials have shown promising results using these drugs in combination with other molecularly targeted therapeutics. The future of epigenetic therapies is considered to be quite promising.

Cell Signaling Targets

As described above, the success of imatinib (Gleevec) guided the development of subsequent drugs that block various components within signaling networks. As a result, 14 chemically based kinase inhibitors have been approved by the FDA to treat an ever-expanding array of cancers (see **Table 2**, pp. 40-41 and **Figure 15**, p. 53), while more are currently in all phases of clinical trials, and still others are in the final stages of approval**.**

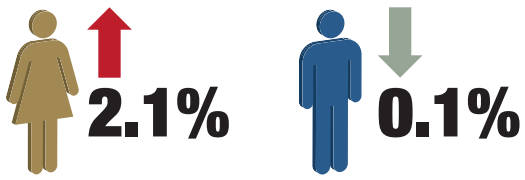
Among these are 3 FDA-approved drugs for patients with CML in which the tumors have a specific chromosomal translocation, called the Philadelphia chromosome, that makes the BCR-Abl kinase. For these patients who comprise 95% of all CML patients, these drugs, which are now the standard of care, have transformed a cancer diagnosis that was previously a death sentence into one with a 5-year survival of 86%. More recently, they have also been found to

be effective in the 5% of pediatric and 25% of adult acute lymphoblastic leukemia (ALL) patients who also have this chromosomal translocation.

Further, 2 FDA-approved kinase inhibitors are now the standard of care for non-small cell lung cancer; 4 are now used to treat renal cell carcinoma; 2 each are used to treat gastrointestinal stromal tumors and pancreatic neuroendocrine tumors; and 1 each are used to treat metastatic breast cancers and medullary thyroid cancers. Additionally, a very unique small molecule inhibitor, called bortezomib (Velcade), is now the standard of care for patients with multiple myeloma. This interesting drug works by blocking the breakdown of proteins, which leads to the disruption of multiple pathways that are necessary for tumor cell proliferation.

The small molecule inhibitors, like imatinib (Gleevec), dasatinib (Sprycel), and nilotinib (Tasigna) have rendered all but a few blood cancers chronic rather than lethal conditions. Unfortunately, for many patients with solid malignancies, these new precision drugs are used to treat their disease after it has already progressed on less precise therapies (see **Table 2**, pp. 40-41). However, these new, more precise drugs provide new hope for long-term survival. With more progress, it is likely that, in the near future, precision therapies like the ones described here will be the first choice of treatment for all appropriate patients.

DEATH RATES FOR PANCREAS (1990-2006)



EST. 2011 INCIDENCE = **44,030** • DEATHS = **37,660**

Andrew Messinger

Age 59
Short Hills, N.J.

In 2005, I was diagnosed with melanoma. It happened after my doctor found a protruding lesion on my chest and reluctantly had it biopsied. After it proved to be melanoma, he referred me for surgery and my first consultation at Memorial Sloan-Kettering Cancer Center. At this point, my scans did not show signs of any metastases in my body.

A month later the lesion was surgically removed, and I spoke with multiple doctors to get opinions on which therapy to pursue. The data were confusing, but I made my decision: interferon. The first night after the initial drug infusion was the most painful and difficult I would experience over the next six years. However, the hospital staff learned how to reduce the side effects, and after a month as an outpatient, I continued with a year of interferon self-injection and scans.

By 2007, however, scans showed lesions on my lung, and I consulted chest surgeons. Surgery revealed additional disease cancer in nearby lymph nodes as well. Still grasping for any way to try to slow the disease, I went on a medication that stimulates the production of blood cells that would hopefully fight off the melanoma, even though it is not FDA approved by the U.S. Food and Drug Administration (FDA) for the treatment of melanoma. I did well for several months on the therapy, known as granulocyte-macrophage colony-stimulating factor, or GM-CSF, until additional lesions on my lungs were detected.

In early 2008, things started to look up. I began four rounds of interleukin-2, or IL-2, and the lesions shrank measurably. I was generally encouraged. The constant therapy was very demanding, but at the time few other treatment options were available. Meanwhile, talk of a new drug, ipilimumab ("ipi"), was spreading. Fortunately for me, the melanoma was not.

But by 2009, scans showed new tumors in my lungs, and for the first time, a brain lesion. At my doctor's suggestion, I immediately joined a small clinical trial to study the effectiveness of ipi on brain lesions. I experienced side effects and actually missed a round of treatment as a consequence, but scans quickly showed that my lung metastases had stabilized, even though ipi was ineffective on my brain lesion. I underwent radio-surgery for the brain lesion and the ipi has kept the metastases in my lungs stable with manageable side effects. Going into the last few ipi infusions on my two-year trial I remain tremendously encouraged. Because of my experience and the experience of other patients like me, ipilimumab (Yervoy) was FDA-approved in April. Ipilimumab is an antibody that re-activates your immune system so that it can help clear your melanoma, see **Harnessing the Patient's Immune System**, p. 59.

I could easily dismiss my three prior treatments as unsuccessful because my disease kept progressing. However, they helped me get to ipi. One major take-away from my experience is that patients should absolutely accept the argument that even in the face of a tough prognosis, the situation can change very quickly. And treatments that offer what is seemingly only incremental survival might actually be the ticket to longer-term success, because they may get you to the treatment that ultimately works.

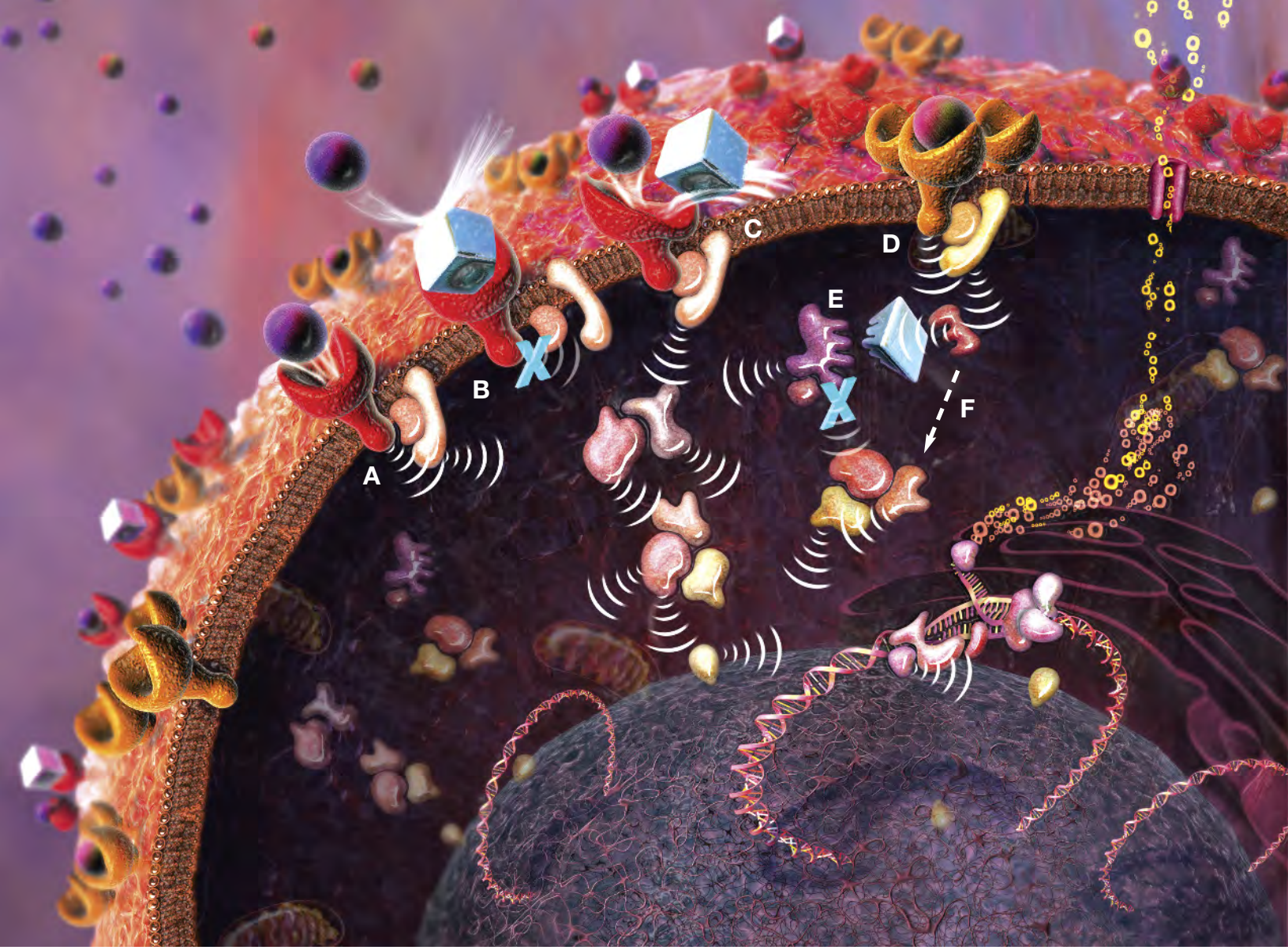


Figure 17: Drug Resistance. A growth factor (purple ball) is depicted driving a cancer cell via interacting with its receptor (A and D). Once this anomaly is identified, the patient is given a drug (B and E), such as a therapeutic antibody (B) or small molecule inhibitor (E), to specifically block this network and shut it off. Either due to primary or acquired resistance, a change in the receptor (red cup-like structure) has made the tumor cell resistant to the drug, turning the network on again (C). Likewise, due to redundancies within the signaling network, tumor cells can continue to use other paths within the network (F) to get around the drug (E).

While the above-mentioned drugs work by targeting components inside cells, signaling networks can also be blocked from outside the cell, which is achieved by using drugs, called therapeutic antibodies. For patients with non-Hodgkin's lymphoma, the first-in-class rituximab (Rituxan), which targets a blood cell-specific surface protein, was a great advance. Trastuzumab (Herceptin), which is used to treat the approximately 20% of breast tumors that are HER2-positive, has improved survival for these women by about 24% (meet cancer survivor and trastuzumab patient **Bonnie Olsen**, p. 56)[28]. For those patients with EGFR-expressing metastatic colorectal cancer, panitumumab (Vectabix) expands their treatment options (see **Table 3**, p. 42).

Targeting the Cancer Cell's Environment

Clinical experience has taught us that targeting cancer cells alone is not sufficient to completely treat a patient's cancer. Fundamental research has identified that the tissue surrounding the tumor plays a role in cancer progression, thus offering new drug targets including the tumor vasculature and the immune system.

The Tumor Vasculature

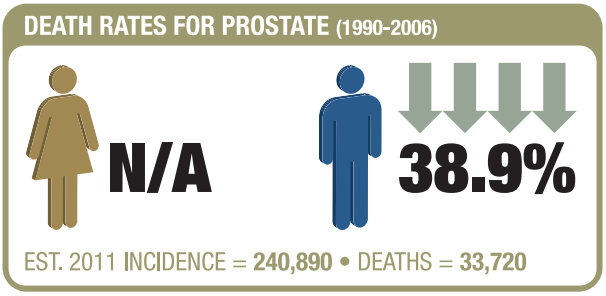
Five FDA-approved drugs work by blocking the growth of the new blood and lymphatic vessels that a tumor needs to grow and thrive; these are now regularly used to treat patients

with renal cell carcinoma, medullary thyroid cancer, gastrointestinal stromal tumors, non-small cell lung cancer, metastatic colorectal cancer, and pancreatic neuroendocrine tumors (see **Figure 4**, and **Tables 2** and **3**, pp. 24, 40-41, 42, respectively)**.** Clinical trials are now underway to determine if other types of cancers can be effectively treated with these therapies.

Harnessing the Patient's Immune System

Recently, it was discovered that many cancers are able to inactivate a patient's immune system (see **Figure 6**, p. 29). This finding led to the development of the therapeutic antibody, ipilumumab (Yervoy), which helps to re-activate the patient's immune cells (meet cancer survivor and ipilumumab patient **Andrew Messinger**, p. 57). This drug is a new and welcomed advance for patients with metastatic melanoma, an aggressive type of skin cancer with few active treatment options. Clinical trials are now underway to test its effectiveness for the treatment of prostate and non-small cell lung cancer.

Immunotherapy, using a vaccine to program the immune system to attack cancer cells, is another new development. The cancer vaccine, sipuluecel-T (Provenge), is now being used to treat patients with metastatic prostate cancer. This strategy is currently being studied in a number of clinical trials to see if it is effective against other cancers. Finally, other immunotherapeutic strategies are in their early stages of development and are showing great promise (meet cancer survivor and immunotherapy patient **Roslyn Meyer**, p. 59).



In the summer of 2005, I discovered a pea-sized lump beside my left ear, and an MRI revealed cancer in my parotid gland and a nearby lymph node. Biopsies suggested an aggressive head and neck cancer, but a full-body PET scan showed a malignancy in my liver as well. A liver biopsy determined that the tumors were actually melanoma. I was 56, married with three children in their 20s. Full of life, despite the terrifying prognosis of stage IV metastatic melanoma, I was determined to fight.

My husband and I consulted a melanoma expert who suggested that I try to get into a clinical trial for a treatment known as adoptive immunotherapy or TIL therapy. TIL, which stands for "tumor-infiltrating lymphocytes," attempts to harness the body's own immune system to recognize and kill cancer cells. At the National Cancer Institute, where this experimental trial was being conducted, doctors would remove my cancerous lymph node and isolate white blood cells, or lymphocytes, that recognized and were attacking my tumor. The researchers would clone these cells, and try to grow billions of them. Finally, the doctors would return this powerful army of cells to my body, where they would fight my cancer. After a number of tests, I was found eligible for the clinical trial, and I enrolled in October 2005.

I entered the hospital and had my cancerous lymph node removed, and the doctors tried—unsuccessfully—to grow the cells for the TIL treatment. (They are currently unable to grow the cells from about 40% of patients.) But while they waited to see if the cells would grow, they put me on high-dose interleukin-2 (IL-2). IL-2 is a tough treatment, and as few as 10 to 20% of people have a favorable response to it. I was one of the lucky ones, and it caused my tumors to shrink. I hoped perhaps I would be one of the few who would be cured, but that was not to be. Over the next 3 years I rode a roller coaster of recurrence and multiple surgeries, but I believed that anything that gives you a chance to live another year, or another month, may mean that a successful treatment could be developed by the time you need it.

I needed such a breakthrough in August 2008, when, to my horror, dozens of tumors appeared in my abdomen. Although the scientists had not been able to grow my cells for TIL therapy that first time in 2005, tumor tissue from my later surgeries allowed them to succeed in 2008, and I was the first person to get a particular variation of the TIL treatment at the National Cancer Institute. The researchers hoped this new variation would be as successful as it had been in animal testing. But it had never been tried in people.

One of the most moving moments for my family was the day the technicians brought in the cells they had been lovingly growing for weeks, along with a card signed by all of them wishing me health and luck. An amazing 84.6 billion cells were infused back into my body along with more IL-2 (see **Harnessing the Patient's Immune System**, p. 59). My children, husband, and I did a little war dance around the I.V. pole. "Go cells, *GO*," I said to myself.

I was in the hospital for almost a month, and the treatment was very difficult. But by March 2009, all of the tumors except one had disappeared. My doctor recommended removing it surgically, so we did. The pathology report showed no live tumor cells. We were ecstatic! It has now been 3 years since I received the TIL therapy, and I continue to have no signs of cancer. The doctors are hopeful that the melanoma will not recur. Although I have been fortunate, and this type of immunotherapy is a very active area of research, it is not yet a typical treatment. It is currently being pursued as a clinical trial at the National Cancer Institute and at The University of Texas MD Anderson Cancer Center in Houston.

So what wisdom can I share from my experiences? Educate yourself about clinical trials, because cancer science is evolving every day. Know all of your options before proceeding. Become an advocate for yourself and others. And never give up hope.

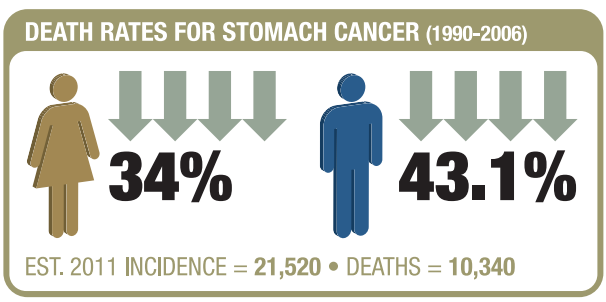
These clinical advances are the direct result of our increased understanding of cancer biology and our current ability to develop drugs that specifically target these processes. This approach has made it possible to develop entirely new classes of drugs that are more effective and less toxic than the treatments that have been the mainstay of patient care for many years.

Tumor Heterogeneity and Its Effect on the Response to Cancer Therapy

The complexity of cancer at the level of an individual tumor is the root cause of our failure to completely eliminate many tumors with current drug therapy.

Over the past 40 years, we have learned that a single tumor contains many subpopulations of cancer cells, meaning that a tumor is heterogeneous. The rapid pace of cell division, coupled with the malfunctioning DNA repair systems of cancer cells, results in unstable and error-prone genomes; together, these are the primary drivers of tumor heterogeneity.

As a result, some tumor cell subpopulations may be actively proliferating while others are not; a different subpopulation may contain a genetic alteration leading to rapid proliferation, while another may contain several distinct molecular defects. Heterogeneity is what drives insensitivity to treatment of both cytotoxic and molecularly based therapeutics, a problem that is magnified exponentially when considering both primary and metastatic lesions.



In some cases, a patient's tumor may initially shrink or stop growing in response to a treatment, stop responding to that treatment, and then begin to grow again. Thus, following treatment, some portion of the tumor cells will be eliminated; however, the cells that do not respond to therapy will continue to proliferate and replace the cells that have been eliminated. As such, the entirety of the tumor can become resistant to a therapy that was previously successful; this is known as acquired resistance. This form of resistance can be caused by new mutations within the cancer cells themselves or the inherent redundancy in the signaling networks that cause cancer (see **Drug Resistance Sidebar**, p. 61 and **Figure 17**, p. 58).

In other cases, a patient is resistant to the therapy from the outset, referred to as innate resistance (see **Drug Resistance Sidebar**, p. 61). This occurs when the presence or absence of other genetic mutations, within either the patient's genome or the tumor's genome, modifies the response to therapy. These factors may alter how a patient metabolizes the drug or how effectively a drug hits its target.

Tumor heterogeneity also explains why simultaneously targeting multiple targets within a cancer cell should increase the likelihood of completely eliminating a tumor and simultaneously preventing drug resistance. For example, it is now commonplace to treat a variety of cancers by using a combination of traditional cytotoxic chemotherapies with varying mechanisms, as well as combinations of more traditional drugs with newer molecularly based drugs.

It is now clear that testing for multiple biomarkers will be necessary to predict innate resistance or the development of acquired resistance and therefore response to therapy. The development and use of biomarker signatures will increase the efficacy of an increasingly precise form of therapy. In the

near future, biomarker signatures will be used to identify the most appropriate combination of molecularly based drugs for a given patient or patient population. This can only occur if there is further biomarker development and the regulatory path is cleared for combinations of molecularly based therapeutics.

Molecularly Informed Clinical Trials

The first impact that biomarkers have had on cancer research was in drug development. Now biomarkers are revolutionizing the design of clinical trials required for their approval (see **Figure 12**, p. 48).

A drug that shows promise in laboratory studies is further developed by testing it in clinical trials; these trials are done with patients to determine definitively whether a treatment is safe and effective in humans. The FDA examines these clinical trial data to determine whether the drug meets the standards for approval.

Clinical trials are currently completed sequentially in a series, referred to as Phase I, II, and III clinical trials (see **Figure 13**, p. 50). Phase I trials are the first studies done in humans and are primarily intended to determine safety. Phase II trials continue to test safety and begin to evaluate how well a drug works to treat a specific type of cancer. If a drug, or new combination of drugs, fulfills the aims of these initial studies, then a Phase III clinical trial is initiated to compare the new therapy to the standard of care. Phase III studies involve large numbers of patients who are typically randomized to receive the standard of care or the new experimental treatment.

Historically, it takes many years for cancer clinical trials to determine the efficacy of a particular treatment based on defined endpoints, such as disease-free survival or overall survival. Because of this delay in obtaining the results, researchers are actively using advanced imaging techniques

The Challenge of Drug Resistance in Cancer Treatment

Drug resistance is one of the greatest challenges we face today in cancer treatment. All tumors that are not completely eliminated will, over time, become resistant to a given therapy and continue to progress.

Resistance generally falls into two categories: acquired resistance, which develops during the course of treatment in response to the therapy, and innate resistance, which is inherent at the outset of treatment. Heterogeneity, which means that multiple subtypes of cancer cells exist within a single tumor, is what ultimately drives insensitivity to treatment of both cytotoxic and molecularly based therapeutics.

The unstable and error-prone genome in a tumor may create a mutation in the drug target, called an escape mutation, rendering a drug useless in that subpopulation of cells (see **Figure 17**, p. 58). For example, a subset of CML patients develop resistance to imatinib that is caused by mutations in the BCR-Abl kinase itself, which reduces the ability of the drug to bind to and block kinase activity. Fortunately, advances in research have led to second and third generation drugs that are FDA approved to treat imatinib-resistant patients.

Further, redundancies within the signaling networks that drive tumor cell proliferation can cause cells to become resistant to therapy. In this case, an initial therapeutic agent can block a signaling pathway within a network, but given the pressure to continue proliferating, the cell can use a "detour" around the blockade and continue through the network (see **Figure 17**, p. 58). As a result, researchers have begun testing combinations of targeted cancer drugs to simultaneously block as many escape routes as possible. This approach has worked in the treatment of HIV, and is likely to meet with success in treating cancer.

Molecular classification of tumors enables physicians to treat cancer patients with the most effective therapy for their tumor type, an advance that is now improving the lives of countless cancer patients. Some patients, however, despite having the correct biomarker, may not initially respond to the therapy, which is called innate or primary resistance. This may occur because of genetic mutations present in the tumor itself, or it could be because of a genetic variation within the patient that alters drug activity or metabolism, or a combination of the two.

Nearly 75% of patients with metastatic colorectal cancer have tumors that express the epidermal growth factor receptor. Therefore, the EGFR-targeted therapeutic, cetuximab (Erbitux), should significantly reduce the extent of the disease in these patients, but a subset of these patients does not respond to the drug. This clinical finding led to research showing that patients with a mutated *KRAS* gene do not respond to cetuximab. As a result, patients with metastatic colorectal cancer are routinely tested to see if they have a normal copy of the *KRAS* gene and the EGFR receptor: if they do, cetuximab is now the standard of care.

More work needs to be done to develop therapies that will avoid or overcome drug resistance. Researchers need to continue to make inroads in understanding the various escape routes for the different tumor types, as well as the factors in both the tumor and the patient that lead to drug resistance.

Trastuzumab (Herceptin): An Antibody That Saves Lives

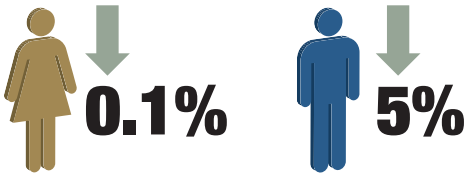
Breast cancer is the second leading cause of cancer-related deaths and the most frequently diagnosed cancer among women. An estimated 232,620 new cases of breast cancer will be diagnosed in 2011[1], and approximately 1 out of every 5 breast cancer cases over-expresses the human epidermal growth factor receptor-2, HER2 gene, and these forms of breast cancer tend to be a more aggressive (see **Bonnie Olsen's Story**, p. 56).

Trastuzumab (Herceptin) is a first of its kind drug that was approved by the FDA to block the activity of the over-expressed HER2. The roots of trastuzumab's success can be traced to our fundamental understanding of oncogenes and cell signaling networks that led to the study and characterization of HER2. The link to human cancer was made in the mid-1980s when HER2 was shown to be present at higher levels in human breast tumors. Studies in a mouse model system provided proof-of-concept that an antibody against the HER2 protein could suppress growth.

Major advances in antibody development fostered the development of trastuzumab, a monoclonal antibody that interacts with the extracellular region of HER2 and blocks the stimulatory signals from the epidermal growth factor (see **Figure 16**, pp. 54-55). Clinical studies began in 1992 and showed increased overall survival for women with HER2-positive metastatic breast cancer; trastuzumab was approved by the FDA in 1998. In 2006, trastuzumab was approved for use after surgery for early stage HER2-positive breast cancer because it reduces the risk of recurrence by up to 24%[28].

Trastuzumab was the first therapeutic antibody to be approved with an associated molecular diagnostic that is used to determine if a patient's should receive the drug. Its impact on cancer continues to grow with the discovery that some tumors in other organs also produce too much of the HER2 protein, including esophagus, uterus, gastrointestinal tract, bladder, and B-cell acute lymphoblastic leukemia. Clinical trials showed a survival benefit when trastuzumab is added to chemotherapy for patients with HER2-positive advanced gastric cancer, leading to FDA approval for this indication in 2010. Clinical trials are now underway to determine whether trastuzumab will also be an effective treatment for other HER2-positive cancers.

DEATH RATES FOR URINARY BLADDER (1990-2006)



EST. 2011 INCIDENCE = **69,250** • DEATHS = **14,990**

to monitor tumor size and number as surrogates for overall and disease-free survival for many tumor types. Surrogate endpoints can decrease the duration of the study, as well as reduce the overall time and cost of bringing new drugs to patients.

Researchers are also actively trying to identify biomarkers that will predict whether a patient is likely to respond to a given treatment. Tumor microarrays have already been shown to predict which breast cancer patients require chemotherapy from those who are unlikely to benefit from its use. Increasingly, clinical trials are measuring biomarkers in tumor tissue and blood collected at the time of surgery to provide a more detailed analysis of trial results and to identify individuals who may best benefit from a particular therapy.

The further evolution of this concept is seen in 2 Phase II proof-of-concept trials, I SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2) and BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination).

In the I SPY 2 trial, experimental therapies are given prior to surgery, and response is determined by a series of MRI images that track tumor size. Patients are genetically screened for a number of biomarkers, and the researchers use that information to generate a common biomarker "signature" for patients who respond to a particular therapy. As the trial progresses, the experience of patients that have completed the trial is used to change the course of the trial while it is still active, rather than waiting until it has completely ended.

The BATTLE trial aims to stratify advanced stage non-small cell lung cancer patients genetically and determine outcomes in real time. This trial randomly assigns non-small cell lung cancer patients to a targeted therapy and then

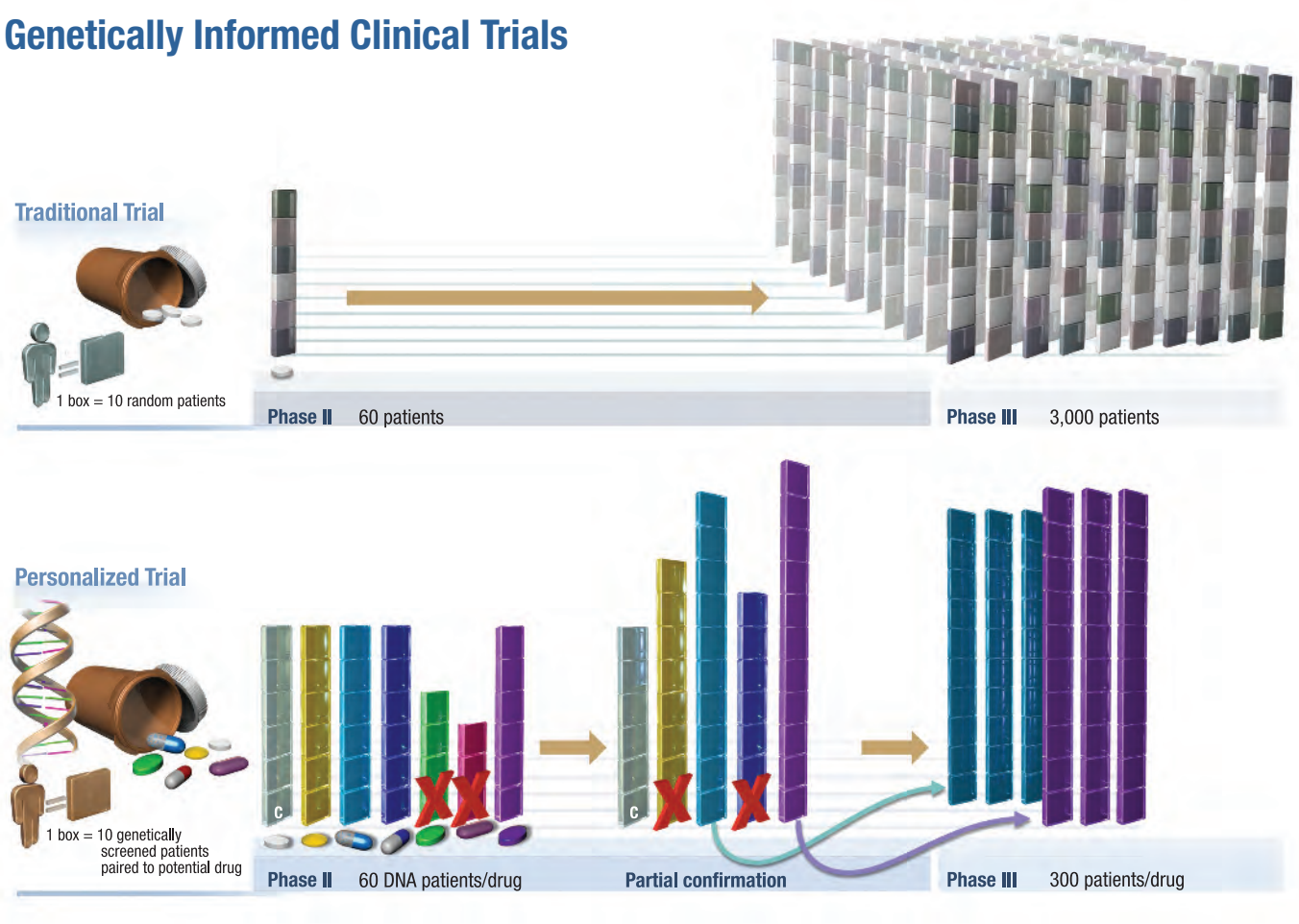


Figure 18: Traditional cancer drug development is slow and leads too often to failures in Phase III trials, which are key components in drug approval. Moreover, traditional Phase III trials are huge and costly. Phase II trials are either single-arm trials evaluating tumor response or small and randomized and have a time-to-event endpoint. In both cases the patient population is assumed to be homogeneous, or the same, even though everyone agrees that it is heterogeneous, or contains multiple subpopulations. The "Personalized Trial" approach, such as taken in I-SPY 2, recognizes the heterogeneous nature of the disease and the possibility that different treatments are effective for different patients. The "trial" is really a phase II drug screening process. Drugs enter the process, are evaluated, and move on. The figure shows 6 experimental drugs, but there could be more. And they enter the trial at different times. The goal is to match experimental treatments with molecular subtypes of disease, or "biomarker signatures." Experimental arms are dropped early (red X) in Phase II if they fail to show efficacy in any subset of disease. In view of the many combinations of treatments and biomarker signatures, for arms suggesting a benefit within a particular signature, that benefit is partially confirmed in Phase II. There are numerous efficiencies in this process that speed drug development, including the simple device of having a common control arm (C). But the major efficiency is enabling a Phase III trial that is an order of magnitude smaller than in the traditional approach because it focuses only on the responding patient population.

follows patient response as a function of their genotype. Early results from this trial suggest that this approach will be successful at linking biomarker signatures to drug response.

Importantly, because of their design, adaptive trials can reduce the number of patients that must be enrolled in order to achieve statistical significance. A large Phase III study may typically need to enroll 3,000 or more patients to obtain enough data to receive FDA approval, whereas only 300 patients may be required in an adaptive trial (see **Figure 18**, p. 63). Utilizing fewer patients per trial is increasingly important because not every targeted therapy will work for every patient. We will continue to witness these advances as modern clinical trial designs are adapted to incorporate biomarkers (see **Figure 12**, p. 48). Validated biomarkers have the potential to transform cancer research and

Cancer Health Disparities in America

Cancer health disparities are differences in the incidence, prevalence, and burden of cancer that exist among specific populations in the U.S., as noted in the table below. Research shows that advances in cancer care do not equally benefit all Americans. Gaps along the entire cancer care continuum—from prevention, to screening and diagnosis, to treatment and follow-up services—are well-documented, most notably among cancer patients from certain racial and ethnic minority groups, individuals with low socioeconomic status, residents in certain geographic locations, the elderly, and individuals from other medically underserved groups (see also **Sidebar on Aging**, p. 65).

Understanding the complex, multifaceted nature of cancer health disparities must continue to be a central component of the Nation's research agenda.

Racial/Ethnic Group	All Sites Incidence	All Sites Death
All	470.1	192.7
African-American	504.1	238.8
American Indian/Alaska Native	297.6	160.4
Asian/Pacific Islander	314.9	115.5
Hispanic/Latino	356.0	129.1
White	477.5	190.7

National Cancer Institute: Statistics are for 2000-2004 and represent the number of new cases of invasive cancer and deaths per year per 100,000 men and women[29].

It is important to consider the following disparities in cancer incidence:

- Lung cancer rates among Southeast Asians are 18% higher than among white Americans. Most cases of lung cancer among East Asian women occur among never smokers, suggesting that genetic and/or environmental risk factors are involved.
- Triple negative breast cancer, a more aggressive cancer for which there are no targeted therapies, accounts for 26% of breast cancer cases in African American women, significantly higher than the 16% of breast cancer among all other ethnicities.
- African American men and women have higher rates of colorectal cancer than their white counterparts (62.1 versus 51.2 per 100,000).
- Hispanic and African American women have a much higher incidence of cervical cancer than white women (13.8 and 11.4 versus 8.5 per 100,000).
- Asian Americans are twice more likely to suffer from liver and stomach cancer than the general population. Korean men experience a rate of stomach cancer 5 times higher than that of white men. Initial studies suggest the higher rates of *H. pylori* infection may explain, in part, why Asian/Pacific Islander populations have higher rates for these cancers.
- American Indian/Alaska Native men are 80% more likely to have liver and intrahepatic bile duct cancer than non-Hispanic white men.
- American Indian/Alaska Native men are nearly twice as likely to have stomach cancer as non-Hispanic white men (15.5 versus 8.8 per 100,000).
- The incidence rate for leukemia, the most common childhood cancer, is approximately 17% higher among Hispanic children, compared to white children.
- American Indians/Alaska Natives have higher rates of kidney and renal pelvis cancer than their white counterparts (14.1 versus 10.2 women; 21.2 versus 20.1 men per 100,000).

Disparities are also apparent in the survival rates of specific populations:

- A 2006 analysis showed that cancer mortality rates in most Appalachian states were higher than the national average of about 181 people out of every 100,000. In fact, 6 of the 7 states with the highest cancer death rates are part of this region (KY-212, MS-211, WV-207, TN-204, AL-199, and OH-198, per 100,000 residents).
- A genetic component related to Native Americans and Hispanics of Native American descent corresponds to a higher rate of relapse during chemotherapy treatment for acute lymphocytic leukemia (24% chance of relapse versus 17% for all patients).
- Although white women tend to have a higher incidence of breast cancer than African- American women (111.8 versus 95.4 per 100,000), the mortality rate is higher among the latter (22.4 versus 33.5 per 100,000).
- African American men have far higher death rates from prostate cancer than any other racial or ethnic group, and are 2.4 times more likely to die of this cancer than white men. Multiple genetic variants have been associated with increased and decreased risks of prostate cancer. Nearly all variants associated with an increased risk of developing prostate cancer were found in African American men, with certain combinations corresponding to a nearly 5-fold increase in risk of prostate cancer in this racial group.
- African Americans suffer the highest rate of colorectal and lung/bronchus cancer deaths (26.7 and 62.0 per 100,000), while Hispanic/Latinos rates are nearly 50% lower (13.6 and 23.6 per 100,000).
- American Indian/Alaska Native men are more than twice as likely to die from stomach cancer as non-Hispanic white men.

The most common factors causing these health disparities are a lack of healthcare access and low socioeconomic status the latter, which is linked to tobacco use, physical inactivity, poor diet, and lower literacy rates. While data suggest that access to care is a key factor, it is also clear that tumor biology, genetics, lifestyle, and environmental exposures also contribute to these disparities. Therefore, it is critical that researchers continue to investigate the reasons for these disparities and develop effective interventions that can mitigate them. We must better understand how all of these factors can be overcome, and develop effective interventions and evidence-based policies to improve prevention strategies and secure access to quality cancer care for all Americans in need.

Should we fail to address this problem, cancer will continue to remain a disease that disproportionately affects certain populations, and the disparities that we see today in a growing U.S. population will become even more pronounced in the future.

dramatically improve patient care; however, in order for these advances to continue at a rapid pace, the challenge of patient enrollment in clinical trials must be addressed. Inadequate patient accrual is a major obstacle to all clinical trials and, in particular, to continued success in the development and approval of molecularly based drugs. Unfortunately, fewer than 5% of adults diagnosed with cancer participate in a clinical trial, despite the fact that clinical trials are an opportunity to receive the latest and most innovative treatments for their disease.

Low patient participation in clinical trials, particularly in underserved and minority populations and geriatric patients, is a major hurdle that must be addressed. There are many reasons why patients do not participate in clinical trials: fear of side effects, lack of awareness, lack of physician awareness or encouragement, bothersome trial requirements, ineligibility, language or cultural barriers, age, and race (see **Aging and Cancer**, p. 65 and **Cancer Disparities Sidebars**, p. 64).

Overall, today's advances in cancer treatment have given us a window into the future of cancer care, and these discoveries are only the beginning. Personalized cancer medicine is still in its early stages of development. As fundamental science continues to provide more molecular information about the biology of cancer, we will witness the further development of unimaginable advances in molecular therapeutics and diagnostic tools, all of which will facilitate the needed precision when choosing the best treatment for an individual patient's cancer.

Molecularly Based Prevention

Our increasing understanding of the unique biological processes of cancer cells has enhanced methods to assign tumors to specific subtypes, enhanced and expanded the process of cancer drug development, and improved patient care. It has also begun to provide a molecular profile of a

Aging and the Development of Cancer

Cancer incidence and prevalence increase with age. Currently, 60% of all cancers occur in the 13% of the population, aged 65 and older. By 2030, this group is estimated to grow to 20% of the U.S. population and account for more than 70% of all new cancer diagnoses[10].

There are 3 primary reasons why cancer is more common in older individuals:

- Cancer is not an event; it is a process that occurs over time. Tissues are exposed to a variety of insults throughout one's lifetime; thus, older tissues have had a longer period in which to accumulate harmful mutations that may cause cancer.
- Due to the lifetime accumulation of acquired mutations in the various cellular repair processes, aging tissues may be more susceptible to the effects of carcinogens later in life because they are unable to effectively repair DNA damage.
- In addition to decreased DNA repair, aging tissues exhibit decreased surveillance by the immune system and increased insulin resistance, all of which may favor the development of cancer.

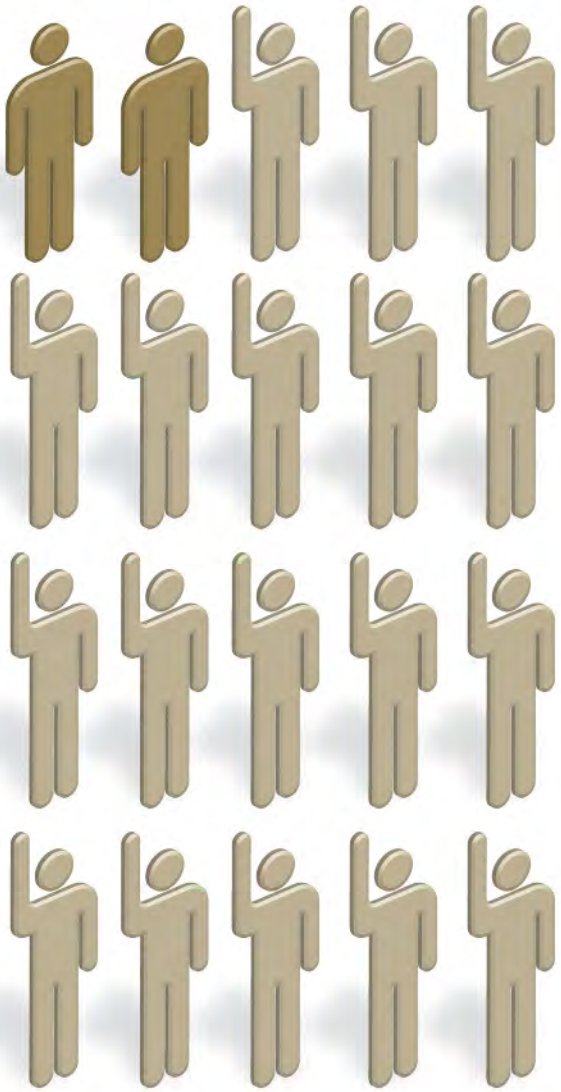
One of the most important advances in cancer care for the elderly has been the development of new tools that can predict how well a patient will respond to chemotherapy. Such tests examine the likelihood of treatment complications, the risk of chemotherapy-related toxicities, and the mortality risk for a given patient, making it easier to choose the appropriate course of treatment. Among these tools are tests that examine leukocyte telomere length and circulating inflammatory markers.

The course of disease is different for younger and older populations, and co-morbidities that tend to accumulate with age also need to be considered when making treatment decisions. For example, elderly patients with acute myelogenous leukemia have a poorer prognosis because their cancer cells are more resistant to chemotherapy than those of younger patients. Interestingly, in the case of some breast cancers, older individuals may have a better prognosis than younger patients because of differences in the tumor microenvironment.

Our ability to successfully treat older patients has advanced with improved surgery and radiotherapy; targeted therapies with limited toxicity; improved palliative care; more protection from chemotherapy-induced mucositis which leads to weight loss and malnutrition; and a better understanding of long-term complications of cancer treatment. In order to continue to improve cancer care for older individuals, we must address the economic, cultural, social, and other factors that have precluded their enrollment in clinical trials. We must also build a large database of elderly patients, as this will allow us to study prognosis and treatment effectiveness in this population for the benefit of all.

Collectively, these advances have increased survival and, importantly, improved the quality of life by facilitating the medical and personal independence of older cancer patients, an increasing component of the U.S. population.

Clinical Trial Participation



Fewer than 5% of adults diagnosed with cancer participate in a clinical trial compared with the over 80% of children that participate, despite the fact that clinical trials are an opportunity to receive the latest and most innovative treatments for their disease. Low patient participation in clinical trials, particularly in underserved and minority populations and geriatric patients, is a major hurdle that must be addressed.

patient's risk of developing cancer that can be used to tailor their individual prevention program.

For example, it is now known that women who have inherited a mutation in one or both of the two tumor suppressor genes, BRCA1 and BRCA2 (BReast Cancer Associated genes 1 and 2), have a 50 to 85% risk of developing breast cancer over their lifetimes, as well as a markedly increased risk of ovarian cancer (meet three-time inherited cancer survivor **Zora Brown**, p. 67). Men who inherit these mutations are also at increased risk of developing breast cancer, and have an increased risk of an aggressive form of prostate cancer. Inherited BRCA mutations are only responsible for about 5 to 10% of all breast and ovarian cancer cases that occur. Currently, however, other genes have been discovered that can be inherited in a mutated form, which confers a marked increase in the risk of developing certain cancers. Unlike these inherited mutations, the vast majority of breast and other cancers are caused by acquired, or somatic, mutations that accumulate during one's lifetime.

Although currently there is no way to correct these inherited cancer gene mutations, the knowledge that individuals are in a high-risk category can induce them to modify their behaviors to reduce risk from other factors, intensify their screening or early detection strategies or, under certain circumstances, consider the option of preventive removal of the organs that are at greatest risk for cancer.

"Educate yourself about clinical trials, because cancer science is evolving every day... Become an advocate for yourself and others. And never give up hope."

Roslyn Meyer
Melanoma Survivor

For me, cancer was a journey that began before I was born. Both my great-grandmother and grandmother were diagnosed with breast cancer at a time when little was known about this disease—and there was little reason for hope.

Mammography had not yet been invented; genetic factors were unknown; radical mastectomy was virtually the only treatment option; and the survival statistics were grim. No one knew what caused breast cancer, so it was something to discuss in whispers. A secret shame.

So much has improved since then, even during my own lifetime. We know today, for example, why cancer has affected 5 generations of women in my family: A genetic mutation of the BRCA1 gene, handed down from mother to daughter, predisposes us to breast and ovarian cancer (see **Molecularly Based Prevention**, p. 65). We also know that, as African-Americans, the women of the Brown family and others like us are at risk for more aggressive cancers that strike earlier and have higher fatality rates (see **Sidebar on Disparities**, p. 64).

Understanding my family and racial histories taught me to be alert and proactive about my health. Although this knowledge did not render me immune from breast cancer, it did facilitate early detection of the disease—first in 1981 when I was just 32, and then again in 1997. That early detection helped me survive and take back my life. As members of a high-risk family, my sisters and I, and now my nieces, have come to understand that we have been given not a genetic curse, but the gift of knowledge and the inspiration to use that knowledge to address the challenges of cancer, and to imbue other survivors with hope.

Now in the midst of my third round with cancer—stage III ovarian cancer, which was detected in 2005—I know all too well what a serious adversary I face. But I also know how to be an advocate for myself, arm myself with information, and surround myself with support and the best that science has to offer.

As a result, I continue to thrive day after day. I have seized the opportunity to take part in a clinical trial for patients who have the BRCA1 gene, and the experience is not only allowing me to receive a cutting-edge treatment, but also to contribute to research that will advance the scientific understanding of cancer and benefit future women like myself.

The Brown women are a living testament to the power of scientific research to significantly reduce the ravages of this insidious disease. Generation by generation, we are evidence of how far medical research has taken us, and I believe in its power to someday put an end to this cycle of disease once and for all.

Adapted from Zora Brown and LaSalle D. Leffall, Jr., MD, 100 Questions & Answers about Breast Cancer, 2003: Jones and Bartlett Publishers, Sudbury, MA. www.jbpub.com.

Cancer Survivorship

An estimated 12 million cancer survivors are alive today in the United States alone, and approximately 15% of these survivors were diagnosed 20 or more years ago. The average 5-year survival rate for all cancers combined has risen consistently, and is now at 68% for adults, and 80% for children and adolescents[3].

These survival statistics reflect major advances in detecting cancers earlier and in better treatments. As these patients are living longer, we are also becoming increasingly aware that cancer therapies can lead to physical, emotional, and psychological problems which might not become apparent in a cancer survivor until 10, 20, or even 30 years after their initial diagnosis and treatment.

Long-term and late effects of radiation include second cancers, endocrine system and thyroid problems, heart disease, and infertility. A person's likelihood of developing these problems depends upon the specific cancer, where the radiation was delivered, and the total radiation dosage received. There are also numerous long-term and late effects of chemotherapy, such as fatigue, infertility, cardiac toxicity, muscle weakness, and cognitive problems.

Perhaps one of the most difficult and serious problems for a cancer survivor is the development of a second cancer. According to the NCI, more than 10% of all invasive cancers that occur each year are second cancers, and some individuals may go on to develop even more cancers.

Given the spectacular success rate for treating many childhood cancers, there has been a great deal of interest in understanding the long-term effects that this particular group of survivors faces. The largest study of adult childhood cancer survivors, the federally funded Childhood Cancer Survivor Study, found that adults who have survived childhood cancer are 3 times more likely than their siblings to develop a later, chronic health condition.

Among this group, 9.6% developed new primary tumors unrelated to their original cancers, and about 30% of this group developed third tumors. This long-term study began in 1993 and has involved more than 14,000 survivors originally diagnosed between 1970 and 1986 at 26 participating research centers in the United States and Canada. Investigators plan to expand the number of participants involved in this study, as well as continue to follow the existing group of survivors as they age.

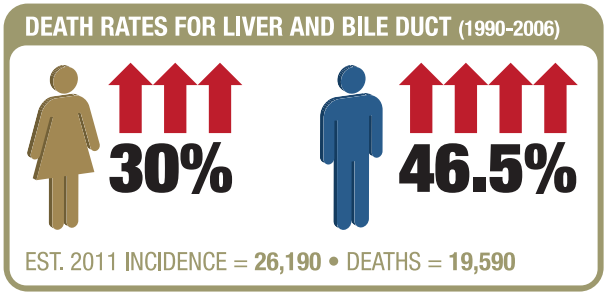
As cancer therapy continues to improve and cancer survivors live longer after diagnosis, the number of persons living with a history of cancer will continue to increase. While middle-aged cancer survivors are most common, in the last 30 years there has been a marked increase in survivorship among the young and old. A new area of research focused on cancer survivorship aims to optimize the health and well-being of men and women living with a history of cancer. Survivorship research must focus on the relationship between aging and cancer, the characterization of the chronic and late effects of cancer therapy, and the development and improvement of patient metrics and care for survivors of all ages.

In addition to behavior modification, increased screening, and preventive surgery, research has given us a new prevention tool, called chemoprevention. Our ability to associate detailed information, including molecular information, about the patient and tumor, with an increase in cancer risk has given rise to the field of chemoprevention, which aims to treat at-risk individuals with a targeted drug to reduce their risk.

One example, although not molecularly based, is in non-small cell lung carcinoma where the cytotoxic chemotherapeutic pemetrexed (Alimta) is an effective maintenance therapy only for those patients that have the non-squamous cell form of lung cancer. Identifying the molecular details about this patient population can only further enhance the precision of this chemopreventive strategy.

In breast cancer, however, the molecular understanding that the hormone, estrogen, drives at least 65% of breast cancers has provided an excellent chemopreventive tool. Two FDA-approved drugs that block the effect of estrogen on its receptor, tamoxifen (Novadex) and raloxifene (Evista), reduce the chance of developing breast cancer by about 50%, or by 38% in women at increased risk, respectively. Further the protective effect can last for years.

Likewise, the non-steroidal anti-inflammatory drug, celecoxib (Celebrex), is FDA-approved to prevent and reduce the formation of colorectal polyps in patients with a high-risk



"We must not lose momentum when breast cancer is the most frequently diagnosed cancer in women."

Bonnie Olsen
Breast Cancer Survivor

genetic condition, called familial adenomatous polyposis (FAP); studies have shown a dose-dependent approximate reduction in the occurrence of polyps between 30 and 50%.

Similarly, finasteride (Proscar), a synthetic anti-androgen agent, has been shown to reduce prostate cancer by 25% in men, aged 55 and older. These are remarkably powerful effects, but we must work even more diligently to identify agents that can effectively prevent the initiation of cancers and that do not themselves have significant side effects. Current preventive agents are effective, but are not widely embraced by physicians and the general public for individuals who have no apparent disease. Using better patient stratification, and incorporating more molecular data about high-risk populations, will ensure the future success of chemoprevention.

Chemoprevention is an important area of research and future opportunity; as such, it has not been overlooked by federal funding agencies. There are approximately 150 chemoprevention clinical trials underway to identify strategies that can be used to reduce cancer incidence in high-risk populations. Continued investment in biomarkers and targeted therapies will result in better matching of high-risk patients to chemopreventive agents in ways that will ultimately tip the risk-benefit scale in favor of these new interventions.

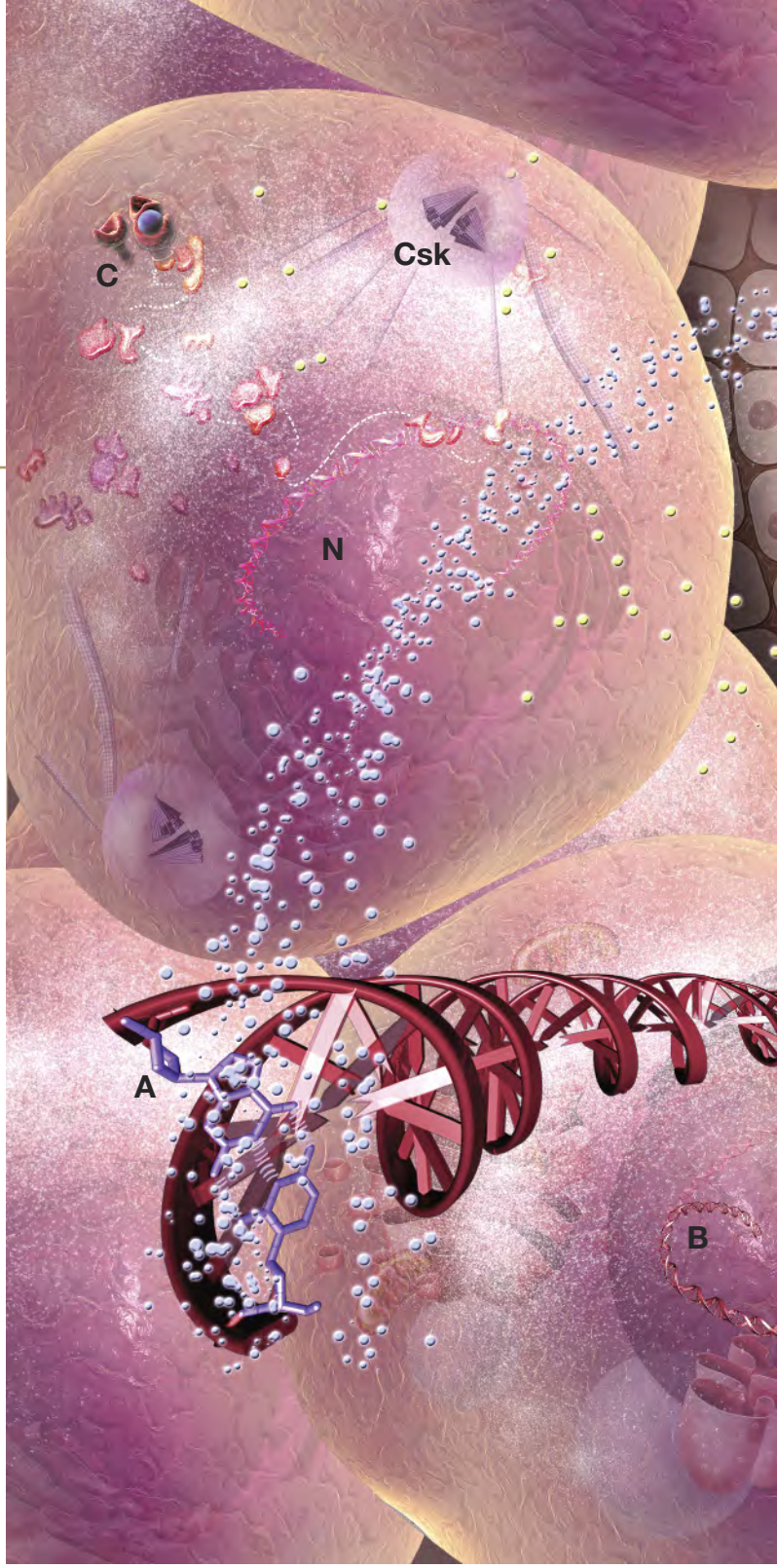
"Genetic studies are leading to better understanding of many cancers and improving our ability to intervene and stop their spread. While the implications of some findings are still unclear, we know that further progress hinges on continued scientific inquiry, and we understand that basic research must remain a national priority."

President William J. Clinton

Cancer Control Month Proclamation, March 29, 1996

The Future:

Fully Realizing the Potential of Our Current Opportunities



Unquestionably, we stand at a defining moment in our Nation's commitment to conquer cancer. The explosion of genetic information and our ever-increasing understanding of how to apply it are providing cancer patients with less toxic and more effective treatment options that are forming the foundation and driving our early successes in personalized medicine.

Personalized cancer medicine, also called molecularly based medicine, precision medicine, or targeted therapy, is moving forward rapidly and has already been integrated into clinical care for some forms of cancer. The successes of some of the targeted drugs listed in **Tables 2**, pp. 40-41 and **3**, p. 42 prove that our deeper understanding of cancer at all levels, particularly the molecular level, can significantly improve patient care.

These advances are a window into a future where all cancer treatment and prevention strategies are based on both a person's own genetic makeup and the genetic makeup of their specific cancer. This vision of the future will require a great deal of innovation in discovery and clinical research, collaboration across all sectors, and a continued fervent commitment from our Nation to tackle cancer.

What Will It Take to Make Personalized Medicine the Standard of Cancer Care?

A Comprehensive Understanding of Cancer

First and foremost, we must continue to pursue a more comprehensive understanding of cancer at all scales, from molecules to cells to man (see **Figure 19**, pp. 70-71).

The convergence of genomic sequencing, including sequencing all of the RNA that will make proteins, and information technologies is providing an unprecedented knowledge of the molecular basis of cancer, which is necessary to pinpoint the vulnerabilities within the different cancers. This new knowledge is essential to uncovering the

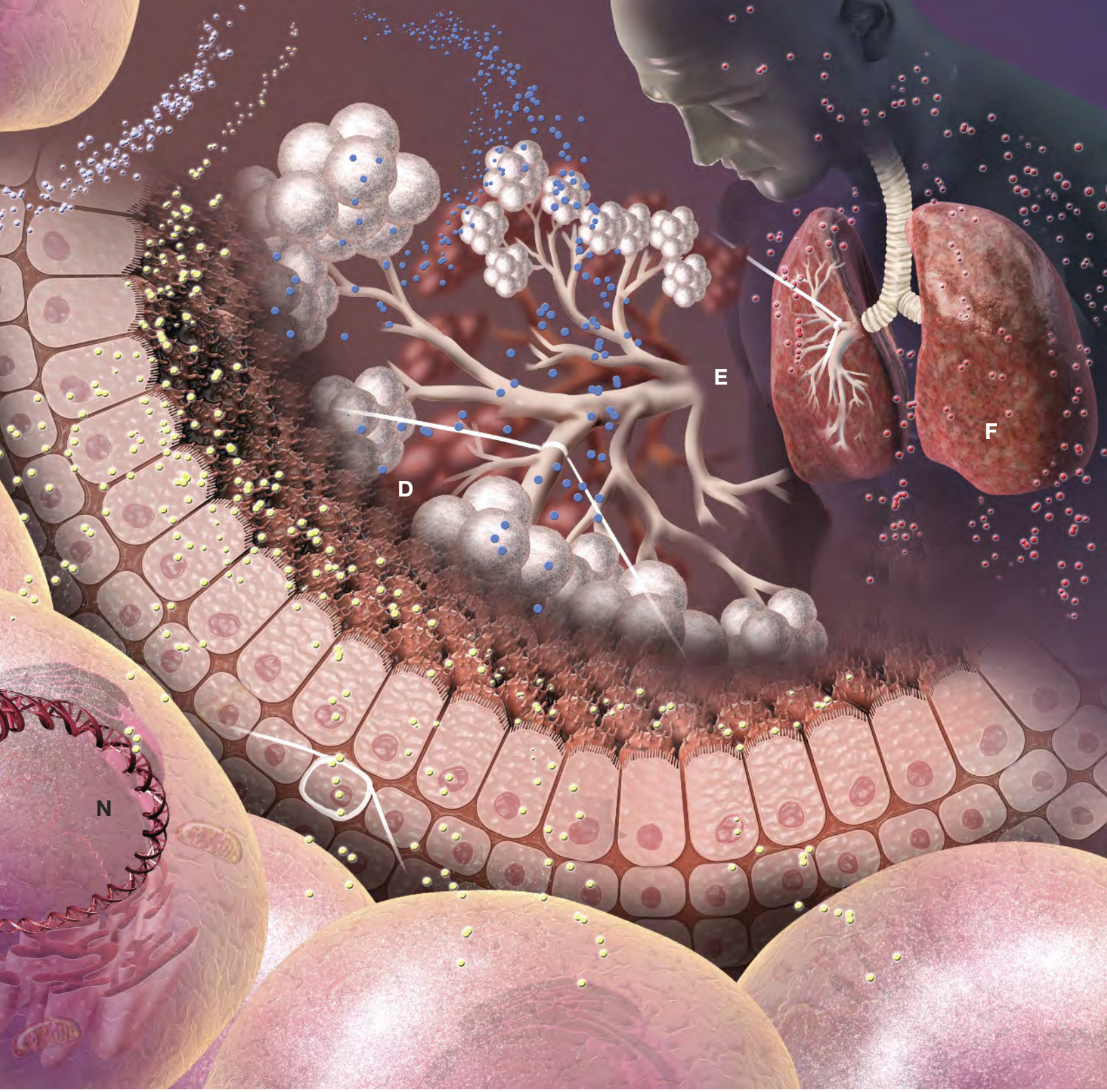


Figure 19: Cancer Occurs and Can Be Treated at Every Scale. DNA, which resides in the nucleus (N) of every cell, is a long chemical chain of building blocks called bases made of two kinds of chemicals, purines and pyrimidines (A). Many cytotoxic chemotherapies (purple dots and Table 2) work by attacking the bases of DNA (A and B) or the cancer cell cytoskeleton (Csk), which is required for cell division. The DNA is organized into genes and chromosomes and its activity is controlled in part by chemical modifications that make up what is known as epigenetics (B). Four different drugs treat cancer by altering these DNA modifications. Activity of the genes within the nucleus (N) of each cell is controlled in part by various signaling pathways (C). Many molecularly-targeted chemotherapies (yellow dots and Tables 1 and 2) work by blocking this signaling. Different types of cells function together with their vasculature, nerves, extracellular matrices, and immune system to form the tissues of the body (D); several molecularly-targeted therapeutics (yellow and blue dots and Tables 1 and 2) function at the tissue level. Finally, various tissues function together to form organs, like the lung (F), tumors at these levels (E and F) are treated best by radiation and/or surgical removal when possible.

Global Collaboration and Multidisciplinary Teams

Cancer and biomedical research increasing require global collaboration. Continued success, will eminate from collaboration at every level: within and between related and unrelated disciplines; within and between related and unrelated departments; within and between institutions; within and between regions, states, countries, and continents. Further, it will require the full cooperation of all stakeholders, including: academia, government, the biotechnology and pharmaceutical industries, philanthropic organizations, patient advocacy groups, and the patients themselves, to ultimately conquer cancer.

biomarkers that will drive the development of highly effective targeted therapies, predict risk for specific cancers, and allow clinicians to develop individual treatment options and prevention strategies for their patients (see **Figure 12**, p. 48).

To deepen our understanding of cancer, our Nation must provide the necessary resources for vitally important research, particularly NIH- and NCI-supported cancer research. For example, we must ensure support for the several large-scale tumor sequencing projects that are beginning and will continue to reveal more molecular information about the subtypes of numerous cancers. Information gleaned from these studies accelerates the development of molecularly based biomarkers, diagnostics, and drugs in the private sector. The development and use of combinations of biomarkers called gene signatures will further increase the efficacy of an increasingly precise form of therapy, not only predicting drug response, but also potential harm.

Due to rapid technological advances, many foresee a time, not far from today, when every cancer patient's tumor will be sequenced prior to treatment. Although necessary, a full genetic understanding of cancer is but one piece of the puzzle. A complete knowledge of cancer at the epigenetic, microenvironment, and systemic levels will also be required in order to see the complete picture.

Our large-scale approaches to probing cancer are producing massive amounts of information that will continue to grow as technologies become increasingly sophisticated. As such, new storage infrastructure, bioinformatics systems, and telecommunications networks are already required to manage our current large data sets, and this need will only increase in the future. It will be necessary not only to manage this increasing volume of information, but also to deliver it to patients and physicians to inform cancer care. Further, the collection and interpretation of this information will only be made possible by multidisciplinary teams of researchers, caregivers in the community, and the patients themselves.

Collaborative Multidisciplinary Teams

Indeed, a more complete picture of cancer will require researchers from the physical, engineering, and mathematical sciences working together with biological and clinical researchers. These multidisciplinary teams represent the convergence of the biological and cancer sciences with the physical sciences, which examine the properties of cancer like thermodynamics, biomechanics, and fluid dynamics in an effort to apply new thinking, computational modeling, and ways of transforming these data into meaningful information regarding cancer cell behavior.

Anticipating the need for the integration of the physical sciences and engineering with the biological sciences, many institutions across the Nation and globally are creating departments that foster collaboration across these once-isolated disciplines. Success in this endeavor will provide even greater opportunities in research, particularly cancer research. We must, however, continue to invest in the training of both current and future generations of researchers to build the multidisciplinary workforce needed to successfully perform this work and yield further advances against cancer.

Although critical to the success of personalized cancer medicine, multidisciplinary teams alone will not be enough. Understanding the multiple complex networks that comprise cancer, ranging from the molecular to the human scale, requires entirely new ways of thinking and models, an approach known as systems biology.

Systems biology is focused on the identification of key networks, pathways within these networks, and interactions

"If we follow our present course—investing in research, translating research findings into medical practice, and increasing access to improved diagnostic and treatment programs—we can continue to make significant progress in our crusade against cancer. We must not slacken our efforts until we can fully control this devastating disease and ultimately eradicate it."

President William J. Clinton

Cancer Control Month Proclamation, March 31, 1998

among the networks that cells use to function normally. Likewise, systems cancer biology seeks to define how these same networks have been deranged so that they now function to support cancer initiation and development. In the near future, new computational and virtual models will map and integrate information from genomics, proteomics (the study of protein interactions), and epigenomics research, along with clinical data, to predict interacting pathways and specifically identify unstable "nodes" that may serve as new targets for cancer intervention, a concept or approach known as computational medicine. The range of new computational methodologies and theoretical models coming from systems biology and computational medicine will most certainly produce more predictive approaches to cancer prevention and treatment that will inform prevention, detection, diagnosis, and treatment.

Advanced Technologies

Advanced technologies have catalyzed unparalleled progress against cancer, and in turn, cancer research has driven innovation in every decade since the Nation seriously turned its attention to conquering what is likely to be the most difficult of all the diseases that mankind has or will ever face. Currently, technologies such as whole genome sequencing, advanced imaging, bioinformatics, and computational models are providing opportunities to understand and rationally control cancer, but our continued success will rely on even newer technologies. Although it is difficult to predict which of the many future technologies or developing areas of research will have the largest impact on cancer research and care, some promising areas are likely to be successful.

One such area that is already having an impact and will likely continue to do so is nanotechnology. This field of science creates and applies new materials with dimensions one million times smaller than a millimeter. By taking advantage of the unique physics of these systems, nanotechnology promises to provide innovative strategies and tools to support molecularly based drug development, drug delivery, highly sensitive and accurate molecularly based diagnostics, and new tools for research, particularly cancer research. Indeed, we have already seen the first glimpses of success with nanotechnology in cancer therapeutics. The FDA-approved drug paclitaxel (Abraxane) is a nanotechnology-based form of the drug taxol used to treat breast cancer.

Another field that promises to greatly inform cancer research and future patient care is stem cells. The significant cellular and genomic heterogeneity of nearly all cancers, even within the same patient, has proven difficult to understand. In fact, it is possible that these distinct cell

"Thirty years of investment in the National Cancer Program following the National Cancer Act of 1971 have accelerated the pace of cancer research. The investment in research has yielded great dividends in the areas of cancer prevention, early detection, better treatments, and improved quality of life for people with cancer. These advances are remarkable, but much remains to be done."

President George W. Bush

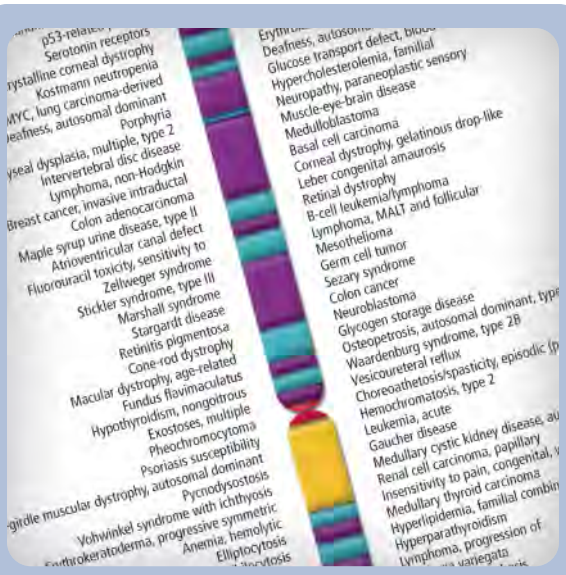
Cancer Control Month Proclamation, March 28, 2001

populations within a given cancer have, in part, fueled drug resistance and made many cancers difficult to treat and control. Stem cells are long-lived cells that can develop into multiple cell types within an organism. Given the behavior of stem cells, it is possible that, for some cancers, stem cells may be the root cause of tumor heterogeneity, resistance to therapy, and tumor dormancy.

Another research area that could significantly contribute to future progress against cancer is cancer metabolism. It has been known for some time that the metabolism of cancer cells is different from normal cells. Researchers have been making progress in understanding and potentially exploiting these differences therapeutically. Interestingly, this area is converging with epigenetics; recent discoveries highlight that several key metabolic enzymes are epigenetically silenced in some cancers. Although in its early stages of exploration, the role of the microbiome, which is the sum total of a person's microorganisms, is an extremely active area of cancer research. The effect of an individual's microbiome could resonate throughout the body and have an impact on areas like metabolism and drug availability.

Similarly, progress in our understanding of regions of the genome that do not make proteins but fine-tune the expression of proteins, like non-coding RNAs, are being implicated in the development of cancer. Further, this area has already provided excellent research tools and may provide therapeutic benefits in the near future. Likewise, newer and more accurate experimental models of cancer will improve the accuracy of preclinical development and the speed at which these findings can be translated into novel therapeutics that save lives.

Many of these technologies and areas of research are focused on producing new therapeutics. Continued research into the science behind behavior modification, as well as the non-invasive diagnostic tools and technologies, could revolutionize our cancer prevention efforts and render cancer treatment a thing of the past.



The $3.8 billion in federal funds invested in the Human Genome Project from 1988 to 2003 helped drive $796 billion in economic impact and generated $244 billion in total personal income, according to a 2011 report by Battelle[30].

In summary, progress in cancer research has enabled a vision for the future in which we understand cancer at a fundamental level and are able to harness the most powerful of emerging and future technologies, along with new approaches of gathering, managing, and interpreting the wealth of information they will provide to achieve personalized medicine. This future is possible and indeed achievable. The U.S. could make no better choice than to continue to invest the resources needed to ensure that cancer is finally controlled for all of its citizens and the world alike.

A Call to Action

Today we are at an important moment in our ability to transform our knowledge of cancer into advances that will dramatically improve the entire spectrum of cancer care, from prevention, early detection, and diagnosis, to treatment and survivorship. It is a period of great optimism about the future, which has been made possible by the decades of federal support for cancer and biomedical research. And, for this commitment, Americans are deeply grateful to our Nation's leaders in Congress and the Executive Branch.

Since the completion of the unprecedented doubling by Congress of the NIH budget in 2003, appropriations for the NIH and NCI have remained essentially flat (see **Biomedical Research and Development Price Index Sidebar**, p. 77). Therefore the NIH has lost about 13% of its purchasing power over the past 8 years due to inflation and the increasing costs of research and technology. For every year of lost purchasing power, less life-saving work is accomplished, and our Nation is losing its long-standing position of global leadership in science and technology.

The Public and Private Sectors Play Different Roles in Research

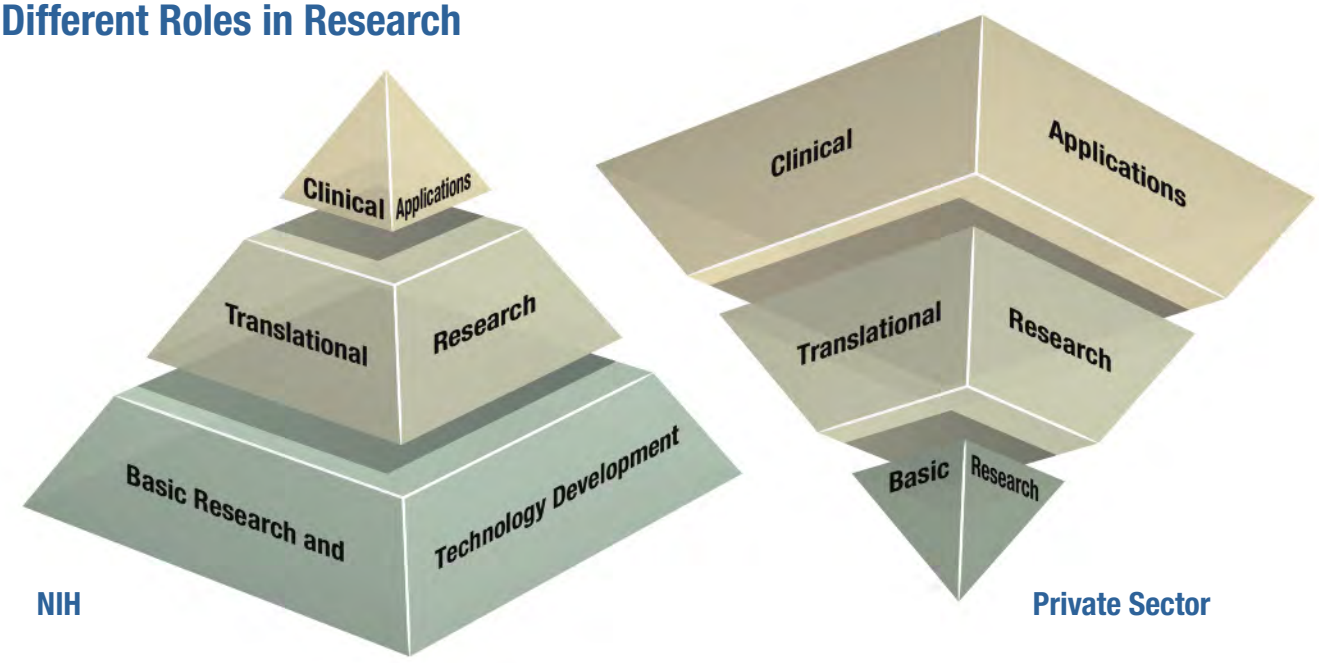
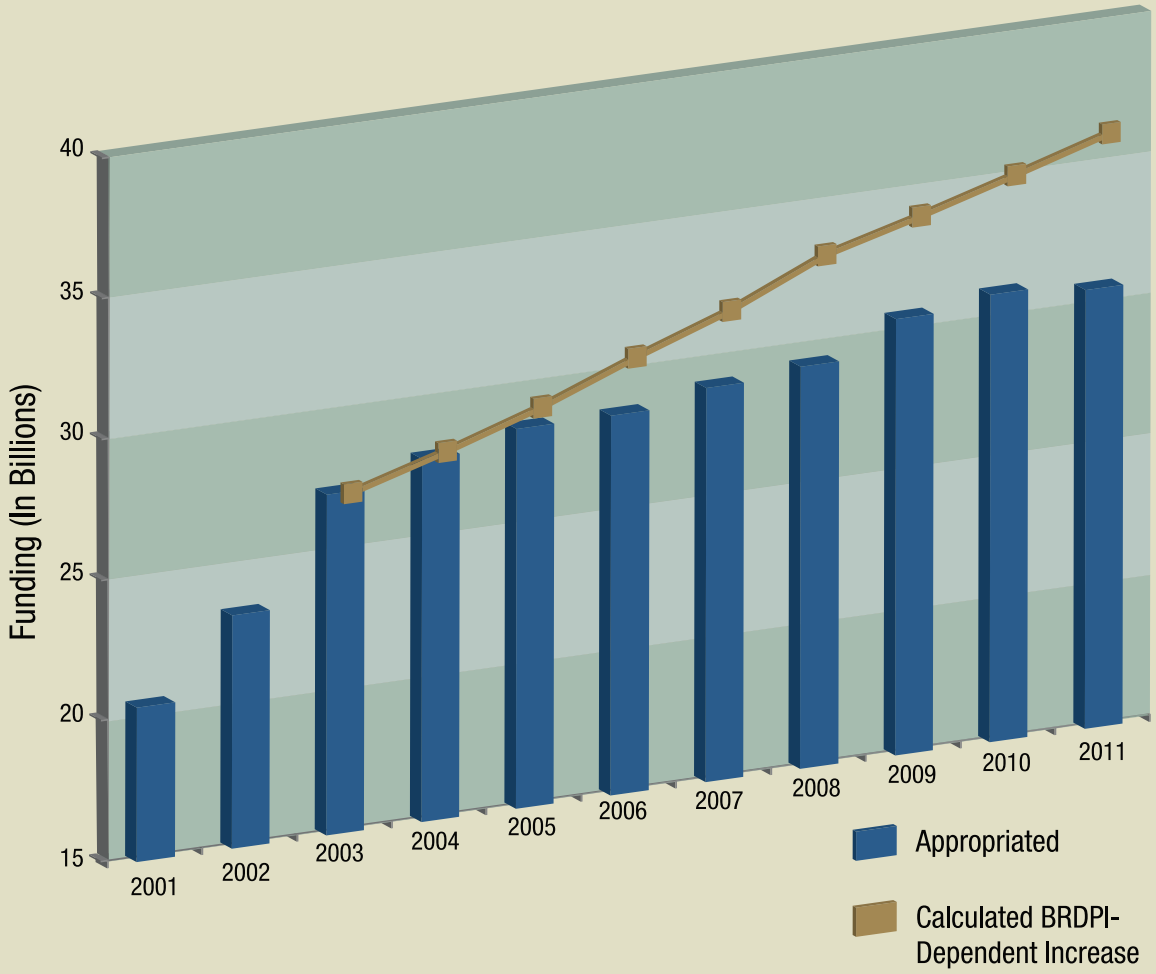


Figure 20: Federal research investments through the NIH complement the investments made by private sector companies and others[31]. The NIH allocates approximately 60% of its budget to basic, or fundamental, research, whereas the private sector spends only 15%. However, the inverse is true for clinical research, where the private sector invests most of its funds and the NIH invests about 15% of its budget. The pyramids are not intended to denote that investments by the NIH and the private sector are equivalent; in 2007, the private sector invested more than double the NIH's investments in research.

Biomedical Research and Development Price Index (BRDPI)



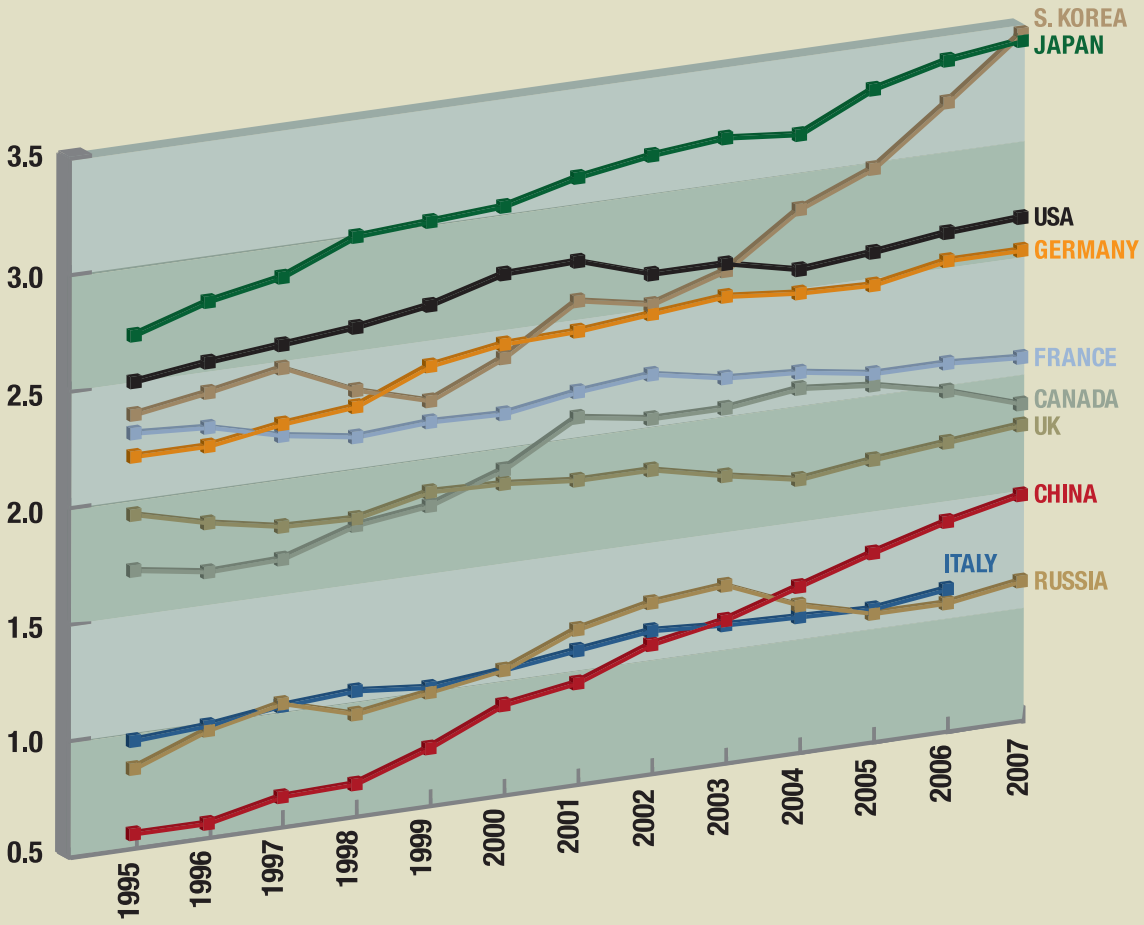
This index reflects the rising cost of personnel, supplies, and equipment needed to conduct research, and indicates how much the NIH budget must increase to maintain purchasing power. The NIH and NCI budgets peaked in FY2003 and have not kept pace with Biomedical Research and Development Price Index (BRDPI). As a result, the NIH and NCI have lost $5.5 billion and $1 billion in purchasing power since FY2003[32].

"In order to win the war against cancer, we must fund the war against cancer."

President George W. Bush

Remarks on Preventive Cancer Screenings, September 18, 2002

National Research and Development Investment (Percent of GDP)



Investment in research and development (R&D) serves as the foundation of innovation. The U.S. R&D investment as a percentage of gross domestic product (GDP) has leveled off in the past decade. At the same time other nations are increasing their investment, most substantially Japan, South Korea, and China. China's investment, for example, has more than doubled from 0.6% in 1996 to 1.5% in 2007[33].

"(we) will launch a new effort to conquer a disease that has touched the life of nearly every American, including me, by seeking a cure for cancer in our time."

President Barack H. Obama

Address to Joint Session of Congress, February 2009

Investments in research, particularly that which are supported by the NIH and NCI, are also important if we are to ensure that a robust scientific workforce is in place and prepared to continue to unravel the complexities of cancer and other diseases for the sake of patients. Because it is known that cancer is a disease of aging, there is an enormous sense of urgency that now is the time to address the cancer problem in America.

Unfortunately, the declining NIH and NCI budgets are creating an environment where researchers face numerous disincentives to continue or even enter into research careers in the first place. These disincentives are resulting in a loss of taxpayer-funded training and are adversely affecting the Nation's ability to maintain an optimal workforce for cancer research and to generate innovative scientific ideas for future implementation.

The NIH, together with its research partners in all sectors of the cancer field, including laboratory scientists, translational researchers, physician-scientists, and survivor and patient advocates, is leading the way in scientific innovations that prevent and cure disease, and extend and improve the quality of life for cancer patients (see **Figure 20**, p. 76). However, without sustained budget increases for research that also takes into consideration inflation and other research expenses, we risk stalling the progress we have already made and compromise our ability to continue to transform cancer care for the benefit of patients.

"We need to continue this trend. If we can extend survival even a few years at a time, then that's a step in the right direction."

Josh Sommer
Chordoma Survivor and Cancer Research Advocate

Investments in research will continue to accelerate progress and promote future advances that will ensure a healthier, more productive future for the millions of men and women in the U.S. and around the world who will be touched by cancer. Funding for cancer and biomedical research at adequate levels will ensure that the U.S. can attract and maintain an optimal scientific workforce. Most importantly, it will reduce the suffering and save lives from cancer, the disease that Americans fear the most.

In order to fulfill the extraordinary scientific and medical promise of cancer and biomedical research, the AACR respectfully recommends that Congress provide the NIH and NCI with annual budget increases of at least 5% above the biomedical inflation rate. This level of sustained support will enable the future scientific advances needed to seize today's scientific momentum, capitalize on prior investments in cancer research, save countless lives, and spur innovation and economic prosperity for our country and all of our citizens. To cross the finish line, to reach the day when cancer is removed as a major health threat to our Nation's citizens, requires that Congress provide critical funding for the life-saving research supported by the NIH and NCI.

References

1. American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society; 2011.
2. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, *et. al.* SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
3. CDC. Cancer Survivors - United States, 2007. *Morb Mortal Wkly Rep* (MMWR). March 11, 2011;60(09):269-272.
4. Centers for Disease Control and Prevention. Smoking & Tobacco Use. May 29, 2009. Trends in Current Cigarette Smoking Among High School Students and Adults, United States, 1965–2007]. Available from: http://www.cdc.gov/tobacco/data_statistics/tables/trends/cig_smoking/index.htm.
5. Centers for Disease Control and Prevention. Cigarette smoking among adults and trends in smoking cessation-United States, 2008. *Morb Mortal Wkly Rep* (MMWR) 2009;58:1227–32.
6. Secretan B, Straif K, Baan R, et al. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; 10:1033–4.
7. Declining Death Rates Reflect Progress against Cancer. Jemal, A., Ward, E., and Thun, M. *PLoS ONE*. 2010;5(3):e9584.
8. http://health.lifegoesstrong.com/heart-vs-cancer
9. http://info.cancerresearchuk.org/news/archive/pressrelease/2010-12-08-cancer-is-biggest-fear-but-some-think-it-is-fate
10. Future of Cancer Incidence in the United States: Burdens Upon an Aging, Changing Nation. Smith, B.D., Smith,G.L., Hurria, A., Hortobagyi, G.N., and Buchholz, T.A. *J Clin Oncol* 2009:2758-2765.
11. World Cancer Report 2008. Lyon (France): IARC; 2008.
12. American Cancer Society. The Global Economic Cost of Cancer; 2010.
13. In Your Own Backyard: How NIH Funding Helps Your State's Economy. A Report from Families USA, June 2008.
14. Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: Detailed Tables; 2009.
15. Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: National Findings. Rockville, MD; 2009.
16. http://www.cancer.gov/cancertopics/factsheet/Risk/radon
17. American Cancer Society perspectives on environmental factors and cancer. Fontham ET, Thun MJ, Ward E, Portier KM, Balch AJ, Delancey JO, *et al.*; ACS Cancer and the Environment Subcommittee.
18. Infectious causes of cancer CA Cancer J Clin. 2009;59(6):343-51. Epub 2009 Oct 28.
19. http://www.cdc.gov/vaccinesafety/vaccines/hpv/gardasil.html
20. Magnetic Resonance Imaging of the Breast Improves Detection of Invasive Cancer, Preinvasive Cancer, and Premalignant Lesions during Surveillance of Women at High Risk for Breast Cancer. Riedl, C.C., Ponhold, L., Flöry, D., Weber, M., Kroiss, R., Wagner, T., *et al.* Clin Cancer Res 2007;13:6144-6152.
21. 2-[^{18}F]Fluoro-2-Deoxyglucose Positron Emission Tomography for the Detection of Disease in Patients with Prostate-Specific Antigen Relapse after Radical Prostatectomy. Schöder, H., Herrmann, K., Gönen, M., Hricak, H., Eberhard, S., Scardino, P., *et al. Clin Cancer Res* 2005;11:4761-4769.
22. Early Response Assessment Using 3'-Deoxy-3'-[^{18}F]Fluorothymidine-Positron Emission Tomography in High-Grade Non-Hodgkin's Lymphoma. Herrmann, K., Wieder, H.A., Buck, A.K., Schöffel, M., Krause, B-J., Fend, F., *et al. Clin Cancer Res* 2007;13:3552-3558.
23. Metabolic Tumor Volume of [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Predicts Short-Term Outcome to Radiotherapy With or Without Chemotherapy in Pharyngeal Cancer. Chung, M.K., Jeong, H-S., Park, S.G., Jang, J.Y., Son, Y-I., Choi, J.Y., *et al. Clin Cancer Res* 2009;15:5861-5868.
24. Mutations of the BRAF gene in human cancer. Davies, H., Bignell, G.R., Cox C., Stephens, P., Edkins, S., Clegg, S., *et al. Nature* 2002;417:949-954.
25. Inhibition of Mutated, Activated BRAF in Metastatic Melanoma. Flaherty, K.T., Puzanov, I., Kim, K.B., Ribas, A., McArthur, G.A., Sosman, J.A., *et al. N Engl J Med* 2010;363:809-19.
26. Comparative Prognostic Value of Epidermal Growth Factor Quantitative Protein Expression Compared with FISH for Head and Neck Squamous Cell Carcinoma. Pectasides, E., Rampias, T., Kountourakis, P., Sasaki, C., Kowalski, D., Fountzilas, G., *et al. Clin Cancer Res* 2011;17:2947-2954.
27. Crystal Structures of the Kinase Domain of c-Abl in Complex with the Small Molecule Inhibitors PD173955 and Imatinib (STI-571). Nagar, B., Bornmann, W.G., Pellicena, P., Schindler, T., Veach, D.R., Miller, W.T., *et al. Cancer Res* 2002;62:4236-4243.
28. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Gianni L, Dafni U, Gelber RD, Azambuja E, Muehlbauer S, Goldhirsch A, *et al. Lancet Oncol* 2011;12(3):236-244.
29. http://www.cancer.gov/cancertopics/factsheet/disparities/cancer-health-disparities
30. Battelle Technology Partnership Practice. Economic Impact of the Human Genome Project. May 2011.
31. Public and private investments in research data: from:http://jama.ama-assn.org/content/303/2/137.full.
32. http://officeofbudget.od.nih.gov/gbiPriceIndexes.html
33. National Science Board. 2010. Science and Engineering Indicators 2010. Arlington, VA: National Science Foundation (NSB 10-01)
34. http://www.cancer.gov/dictionary

Glossary[34]

A-C

Acute lymphoblastic leukemia (ALL) - An aggressive (fast-growing) type of leukemia (blood cancer) in which too many lymphoblasts (immature white blood cells) are found in the blood and bone marrow; also called acute lymphocytic leukemia.

Adjuvant setting/therapy/care – A treatment given in addition to the primary, main or initial treatment. An example of adjuvant therapy is the use of chemotherapy after surgery or radiotherapy where detectable disease has been removed, but where there remains a statistical risk of relapse due to undetectable disease. If known disease is left behind following surgery, then further treatment is not considered to be adjuvant.

Acquired Immunodeficiency Syndrome (AIDS) - A disease caused by the human immunodeficiency virus (HIV). People with AIDS are at an increased risk for developing certain cancers and for infections that usually occur only in individuals with a weak immune system.

Analgesic - A drug that reduces pain. Analgesics include aspirin, acetaminophen, and ibuprofen.

Androgen - A type of hormone that promotes the development and maintenance of male sex characteristics.

Angiogenesis - The formation of blood vessels from pre-existing vascular beds. It is a multistep process that is essential normal function, and plays a role in numerous pathological conditions including cancer development and metastasis.

Anti-emetic - A drug that is effective against vomiting and nausea. Anti-emetics are typically used to treat motion sickness and the side effects of opioid analgesics, general anesthetics, and chemotherapy directed against cancer.

B-cell - A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B-cell is a type of white blood cell; also called B-lymphocyte.

BCR-Abl kinase – A protein made from pieces of two genes that are joined together. It is found in most patients with chronic myelogenous leukemia (CML), and in some patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML). Inside the leukemia cells, the ABL gene from chromosome 9 joins to the BCR gene on chromosome 22 to form the BCR-Abl fusion gene, which makes the BCR-Abl fusion protein.

Bioinformatics - The science of using computers, databases, and mathematics to organize and analyze large amounts of biological, medical, and health information. Information may come from many sources, including patient statistics, tissue specimens, genetics research, and clinical trials.

Biospecimen - Samples of material, such as urine, blood, tissue, cells, DNA, RNA, and protein from humans, animals, or plants. Biospecimens are stored in a biorepository and are used for laboratory research. If the samples are from people, medical information may also be stored along with a written consent to use the samples in laboratory studies.

Biomarker - A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition; also called molecular marker and signature molecule.

Bisphosphonate – A drug or substance used to treat hypercalcemia (abnormally high blood calcium) and bone pain caused by some types of cancer. Forms of bisphosphonates are also used to treat osteoporosis and for bone imaging. Bisphosphonates inhibit a type of bone cell that breaks down bone; also called diphosphonate.

BRCA1/2 (Breast Cancer Resistance Genes 1 and 2) - Genes that normally help to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA1 gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer.

Cancer - A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord; also called malignancy.

Carcinogen - Any substance that causes cancer.

Chemoprevention - The use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of, cancer.

Chemotherapy - The use of different drugs to kill or slow the growth of cancer cells

Chromosome - Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes.

Chronic myelogenous leukemia (CML) - A slowly progressing disease in which too many white blood cells (not lymphocytes) are made in the bone marrow. Also called chronic granulocytic leukemia and chronic myeloid leukemia.

Clinical trial - A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

Clinical trial phase - A part of the clinical research process that answers specific questions about whether treatments that are being studied work and are safe. Phase I trials test the best way to give a new treatment and the best dose. Phase II trials test whether a new treatment has an effect on the disease. Phase III trials compare the results of people taking a new treatment with the results of people taking the standard treatment. Phase IV trials are done using thousands of people after a treatment has been approved and marketed, to check for side effects that were not seen in the Phase III trial.

Colonoscopy - Examination of the inside of the colon using a colonoscope, inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Computed tomography (CT) - A series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an x-ray machine. Also called CAT scan, computerized axial tomography scan, and computerized tomography.

Cutaneous T-cell lymphoma - Any of a group of T-cell non-Hodgkin's lymphomas that begin in the skin as an itchy, red rash that can thicken or form a tumor. The most common types are mycosis fungoides and Sézary syndrome.

Cyberknife - Is a frameless robotic radiosurgery system used for treating benign tumors, malignant tumors and other medical conditions. The system is a method of delivering radiotherapy using a computer, with the intention of targeting the lesion more accurately than standard radiotherapy.

C-H

Cytomegalovirus (CMV) - A virus that may be carried in an inactive state for life by healthy individuals. It is a cause of severe pneumonia in people with a suppressed immune system, such as those undergoing bone marrow transplantation or those with leukemia or lymphoma.

Cytotoxic chemotherapy - Anticancer drug that kills all rapidly dividing cells, especially cancer cells.

Diabetes - Any of several diseases in which the kidneys make a large amount of urine. Diabetes usually refers to diabetes mellitus in which there is also a high level of glucose (a type of sugar) in the blood because the body does not make enough insulin or use it the way it should.

DC-MRI - A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. Magnetic resonance imaging makes better images of organs and soft tissue than other scanning techniques, such as computed tomography (CT) or x-ray. Magnetic resonance imaging is especially useful for imaging the brain, the spine, the soft tissue of joints, and the inside of bones. DC-MRI, uses repeated imaging to track the entrance of diffusible contrast agents into tissue over time.

Death rate/mortality rate - The number of deaths in a certain group of people in a certain period of time. Mortality may be reported for people who have a certain disease, live in one area of the country, or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) – The molecules inside cells that carry genetic information and pass it from one generation to the next.

Drug Resistance - The failure of cancer cells, viruses, or bacteria to respond to a drug used to kill or weaken them. The cells, viruses, or bacteria may be resistant to the drug at the beginning of treatment, or may become resistant after being exposed to the drug.

Epidermal growth factor receptor (EGFR) - The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor; also called ErbB1 and HER1.

Endpoint - In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.

Enzyme - A protein that speeds up chemical reactions in the body.

Epidemiology - The study of the patterns, causes, and control of disease in groups of people.

Epigenetics - The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence. Examples of such changes might be DNA methylation or histone deacetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

Epstein-Barr virus (EBV) - A common virus that remains dormant in most people. It causes infectious mononucleosis and has been associated with certain cancers, including Burkitt's lymphoma, immunoblastic lymphoma, and nasopharyngeal carcinoma.

Extracellular Matrix (ECM) - The proteins outside of cells that usually provide structural support and perform other important functions.

Familial adenomatous polyposis (FAP) - An inherited condition in which numerous polyps (growths that protrude from mucous membranes) form on the inside walls of the colon and rectum. It increases the risk of colorectal cancer; also called familial polyposis.

Gastrointestinal stromal tumor (GIST) - A type of tumor that usually begins in cells in the wall of the gastrointestinal tract, it can be benign or malignant.

Gene - The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Glioblastoma (GBM) - A fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord, and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord. Also called glioblastoma multiforme and grade IV astrocytoma.

Growth factor - A substance made by the body that functions to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy.

Hematopoietic growth factor - A group of proteins that causes blood cells to grow and mature.

Helicobacter pylori (H. pylori) - A type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with Helicobacter pylori infections may be more likely to develop cancer in the stomach, including mucosa-associated lymphoid tissue (MALT) lymphoma.

Hepatitis B virus (HBV) - A virus that causes hepatitis (inflammation of the liver). It is carried and passed to others through the blood and other body fluids. Different ways the virus is spread include sharing needles with an infected person and being stuck accidentally by a needle contaminated with the virus. Infants born to infected mothers may also become infected with the virus. Although many patients who are infected with hepatitis B virus may not have symptoms, long-term infection may lead to cirrhosis (scarring of the liver) and liver cancer.

Hepatitis C virus (HCV) - A virus that causes hepatitis (inflammation of the liver). It is carried and passed to others through the blood and other body fluids. Different ways the virus is spread include sharing needles with an infected person and being stuck accidentally by a needle contaminated with the virus. Infants born to infected mothers may also become infected with the virus. Although patients who are infected with hepatitis C virus may not have symptoms, long-term infection may lead to cirrhosis (scarring of the liver) and liver cancer. These patients may also have an increased risk for certain types of non-Hodgkin's lymphoma.

Heterogeneous/heterogeneity - Made up of elements or ingredients that are not alike.

Human immunodeficiency virus (HIV) - The cause of acquired immunodeficiency syndrome (AIDS).

Hormone - One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

Human papillomavirus (HPV) – A type of virus that can cause abnormal tissue growth (for example, warts) and other changes to cells. Infection for a long time with certain types of human papillomavirus can cause cervical cancer. Human papillomavirus may also play a role in some other types of cancer, such as anal, vaginal, vulvar, penile, oropharyngeal, and squamous cell skin cancers.

Hypercalcemia - Higher than normal levels of calcium in the blood. Some types of cancer increase the risk of hypercalcemia. This condition can occur following metastasis of some cancers to the bone.

Inflammation - Redness, swelling, pain, and/or a feeling of heat in an area of the body. This is a protective reaction to injury, disease, or irritation of the tissues.

Immune system - A diffuse, complex network of interacting cells, cell products, and cell-forming tissues that protects the body from pathogens and other foreign substances, destroys infected and malignant cells, and removes cellular debris. The immune system includes the thymus, spleen, lymph nodes and lymph tissue, stem cells, white blood cells, antibodies, and lymphokines.

Immunotherapy - Treatment designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process, as cancer.

Incidence - The number of new cases of a disease diagnosed each year.

Kinase - A type of enzyme that causes other molecules in the cell to become active. Some kinases work by adding chemicals, called phosphates, to other molecules, such as sugars or proteins. Kinases are a part of many cell processes. Some cancer treatments target certain kinases that are linked to cancer.

KRAS gene - A gene that may cause cancer when it is mutated (changed). The *KRAS* gene makes the K-Ras protein, which is involved in cell signaling pathways, cell growth, and apoptosis (cell death). Agents that block the activity of the mutated *KRAS* gene or its protein may stop the growth of cancer.

Laparoscopy - A procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen. A laparoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Leukemia - Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream.

Lesion - An area of abnormal tissue. A lesion may be benign (not cancer) or malignant (cancer).

Lumpectomy - Surgery to remove abnormal tissue or cancer from the breast and a small amount of normal tissue around it. It is a type of breast-sparing surgery.

Lymphangiogenesis - is the formation of lymphatic vessels from pre-existing lymphatic vessels, using a mechanism similar to blood vessel development or angiogenesis. Lymphangiogenesis plays an important physiological role in homeostasis, metabolism and immunity. Lymphatic vessel formation has also been implicated in a number of pathological conditions including cancer metastasis, edema, rheumatoid arthritis, psoriasis and impaired wound healing.

Lymphatic vessels (system) - The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). Lymphatic vessels branch, like blood vessels, into all the tissues of the body.

Macular degeneration - A condition in which there is a slow breakdown of cells in the center of the retina (the light-sensitive layers of nerve tissue at the back of the eye). This blocks vision in the center of the eye and can cause problems with activities such as reading and driving. Macular degeneration is most often seen in people who are over the age of 50. Also called age-related macular degeneration, AMD, and ARMD.

Mammography - The use of film or a computer to create a picture of the breast.

Mary Lasker - (November 30, 1900 – February 21, 1994) was an American health activist. With her husband Albert Lasker, they transformed the American Cancer Society into an effective advocacy organization, founded the Lasker Foundation, raised record funds for research, and were instrumental in the passage of the 1971 National Cancer Act.

Mastectomy - Surgery to remove the breast (or as much of the breast tissue as possible).

Medullary thyroid cancer - Cancer that develops in C cells of the thyroid. The C cells make a hormone (calcitonin) that helps maintain a healthy level of calcium in the blood.

Melanoma - A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.

Metastasis - The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a "metastatic tumor" or a "metastasis." The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

Microbiome - A microbiome is the totality of microbes, or microorganisms, their genomes, and environmental interactions in a defined environment. The human microbiome contains over 10 times more microbes than human cells.

Multiple myeloma - A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

Mutation - Any change in the DNA of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

Myelodysplastic syndrome (MDS) - A group of diseases in which the bone marrow does not make enough healthy blood cells. Also called preleukemia and smoldering leukemia.

Nanotechnology - A technology executed on the scale 1000 times smaller than a millimeter, the goal of which is to control individual atoms and molecules, especially to create computer chips and other microscopic devices.

Neoadjuvant therapy - Treatment given as a first step to shrink a tumor before the main treatment is given, which is usually surgery. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.

Non-small cell lung carcinoma - A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Non-small cell lung cancer is the most common kind of lung cancer.

Oncogene - A gene that is a mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or caused by being exposed to substances in the environment that cause cancer.

P-Z

Palliative care - Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of palliative care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, supportive care, and symptom management.

Papanicolaou or PAP test - A test of a sample of cells taken from a woman's cervix. The test is used to look for changes in the cells of the cervix that show cervical cancer or conditions that may develop into cancer. It is the best tool to detect precancerous conditions and hidden, small tumors that may ultimately develop into cervical cancer.

Pancreatic neuroendocrine tumor - A rare cancer that forms in the islets of Langerhans cells (a type of cell found in the pancreas). Also called islet cell carcinoma.

Philadelphia chromosome - An abnormality of chromosome 22 in which part of chromosome 9 is transferred to it. Bone marrow cells that contain the Philadelphia chromosome are often found in chronic myelogenous leukemia.

Polyp - A benign growth that protrudes from a mucous membrane.

Positron emission tomography (PET) - A procedure in which a small amount of radioactive dye (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the dye travels; also called PET scan. Because cancer cells often use more glucose than normal cells, when combined with a radioactive glucose (sugar) called FDG, the pictures can be used to find cancer cells in the body, including micrometastases; this type of procedure is called FDG-PET.

Prevalence - the number or percent of people alive on a certain date in a population who previously had a diagnosis of the disease. It includes new (incidence) and pre-existing cases, and is a function of both past incidence and survival.

Prostatic Specific Antigen (PSA) - An enzyme secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Protein - A molecule made up of amino acids that are needed for the body to function properly. Proteins are the basis of body structures, such as skin and hair, and of substances such as enzymes, cytokines, and antibodies.

Radiation - Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical x-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radiotherapy - The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body; also called irradiation and radiation therapy.

Renal cell carcinoma - The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. The renal tubules filter the blood and produce urine. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

Rheumatoid arthritis (RA) - An autoimmune disease that causes pain, swelling, and stiffness in the joints, and may cause severe joint damage, loss of function, and disability. The disease may last from months to a lifetime, and symptoms may improve and worsen over time. Some cancer therapeutics are now routinely used for the treatment of RA.

Signaling pathway/signaling network - A group of molecules in a cell that work together to control one or more cell functions, such as cell division or cell death. After the first molecule in a pathway receives a signal, it activates another molecule. This process is repeated until the last molecule is activated and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. This may help block cancer cell growth and kill cancer cells.

Stereotactic radiosurgery - A type of external radiation therapy that uses special equipment to position the patient and precisely give a single large dose of radiation to a tumor. It is used to treat brain tumors and other brain disorders that cannot be treated by regular surgery. It is also being studied in the treatment of other types of cancer. Also called radiation surgery, radiosurgery, and stereotaxic radiosurgery.

Surrogate endpoint - A biomarker intended to substitute for a clinical endpoint (see **Endpoint**). Surrogate markers are used when the primary endpoint is undesired (e.g., death), or when the number of events is very small, thus making it impractical to conduct a clinical trial to gather a statistically significant number of endpoints. The FDA and other regulatory agencies will often accept evidence from clinical trials that show a direct clinical benefit to surrogate markers.

The Cancer Genome Atlas (TCGA) - A project to catalogue genetic mutations responsible for cancer, started in 2005. The goal of the project is to provide systematic, comprehensive genomic characterization and sequence analysis of different types of human cancers.

Tumor - An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer), or malignant (cancer); also called neoplasm.

Tumor microenvironment - The normal cells, molecules, and blood vessels that surround and feed a tumor cell. A tumor can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

Tumor suppressor gene - A type of gene that makes a protein called a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer;also called an antioncogene.

Vaccine - A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

Vaccine/Immunotherapy - A type of treatment that uses a substance or group of substances to stimulate the immune system to destroy a tumor or infectious microorganisms such as bacteria or viruses.

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American Association for Cancer Research

615 Chestnut Street, 17th Floor • Philadelphia, PA 19106-4404 • 215-440-9300 • govrelations@aacr.org • www.aacr.org